NUTRITIONAL AND
VITAMIN THERAPY
IN
GENERAL
PRACTICE

· · ·EDGAR S. GORDON· · ·

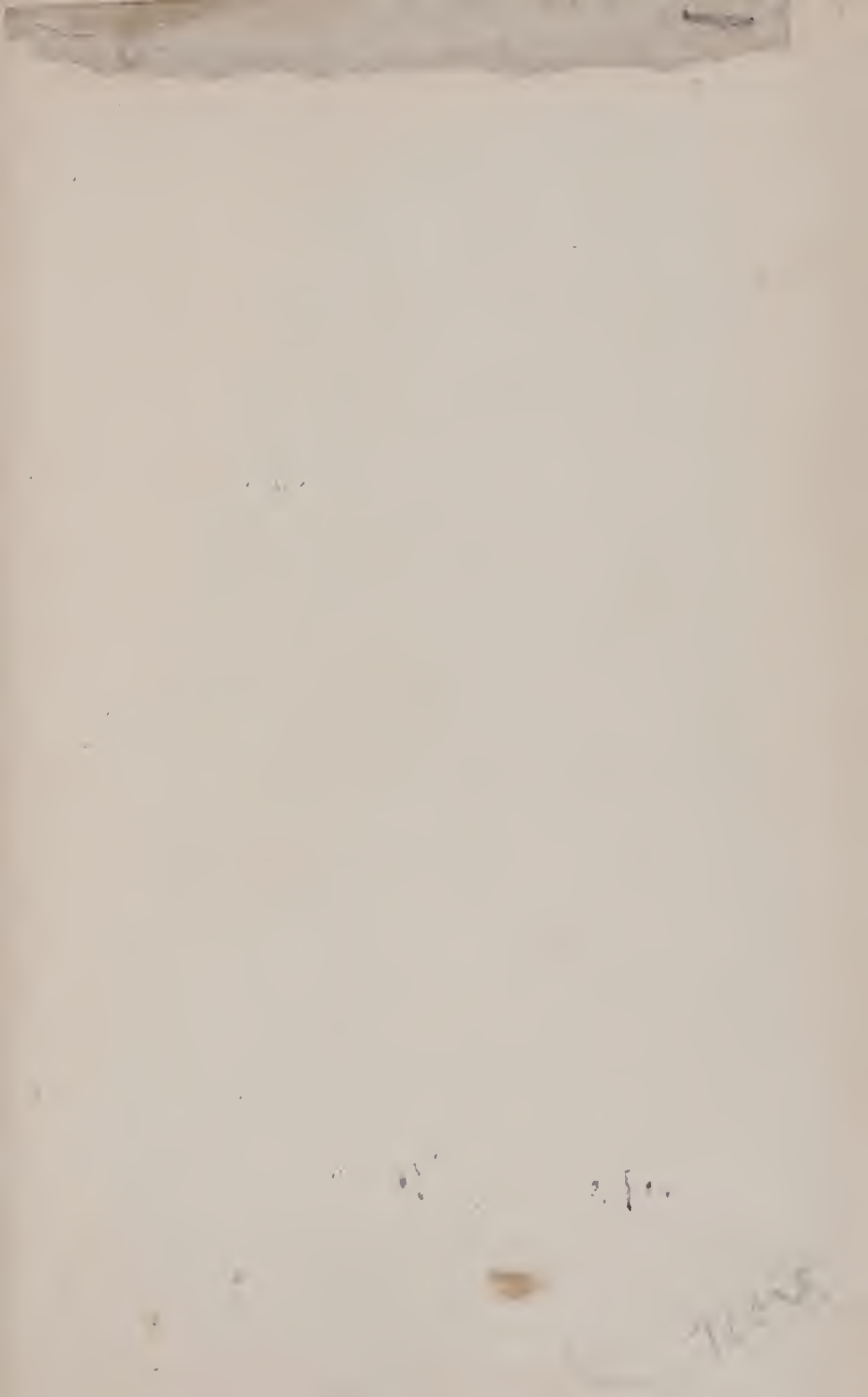## THIRD
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NUTRITIONAL AND VITAMIN THERAPY IN GENERAL PRACTICE

Nutritional and Vitamin Therapy in General Practice

By

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To

Elmer L. Sevringhaus

Close friend, able physician and brilliant scientist,
who was my most valued advisor and critic
for many years.

FOREWORD

Far-reaching advances have been made in the field of nutrition during the past two decades. More and more diseases are being associated with dietary deficiencies, especially with inadequate supplies of certain vitamins. There is evidence from animal experimentation that the individual vitamins may soon reach 20 in number. At present 10 vitamins are available in pure form; in practically every case a specific deficiency disease in humans has been associated with an inadequate intake of each of these factors.

The availability of synthetic vitamins is of distinct advantage in the treatment of acute deficiencies. The dramatic responses which have been obtained through the use of some of the pure preparations are familiar to every practitioner. However, the physician must be more alert than ever before in his diagnosis, since any one vitamin can relieve the symptoms resulting from a lack of only that specific factor. The crude concentrates which are gradually being replaced by the purer vitamins are perhaps less effective in speed of action, but certainly more valuable in multiple deficiencies.

Advances in the field of nutrition have been so rapid that it is difficult even for those working ex-

clusively in the field to keep abreast of the newer findings, to say nothing of those interested in the entire field of medicine. Many physicians would like to follow the experimental results as they develop but find that time will not permit. The best substitute is the availability of the important information in concise form prepared by men who are familiar with both the fundamental and the practical aspects of nutrition. This book adequately fills this need. The emphasis on the quantitative aspects of the distribution and requirements of the various nutrients is most attractive and should be of great help in the successful use of the known vitamins. Proper use of this information should aid greatly in the reduction of deficiency diseases to the point where the administration of synthetic vitamins in acute deficiencies will rarely be necessary. It is my hope that information concerning the unknown vitamins will continue to be elucidated as rapidly as has been that concerning the vitamins we can call by name, and that future editions of this book will carry such new information.

—C. A. ELVEHJEM

Madison, Wis.
July 1, 1940

PREFACE TO THE THIRD EDITION

Four years of war and world-wide turmoil have intervened since the preparation of the last edition of this volume. As a part of the evolution of the concept of total war there has emerged the realization that not only armies but whole civilian populations must be adequately cared for and properly nourished if they are to maintain the capacity and will to carry on the struggle. Appreciation of this fact at the outset led each of the belligerent nations to place a new emphasis on the accumulation of vast food stores, to regard with new enthusiasm and concern the preservation of the integrity of agriculture and to guarantee the maintenance of practical investigation in the field of nutrition. Thus, dictated by stern necessity, important new contributions have been made in this field which unquestionably played a vital part in the prosecution and outcome of the war.

Even with hostilities ended, as an aftermath of war there exist widespread malnutrition and mass starvation generally distributed over the face of the globe but concentrated naturally in those areas most closely involved in the physical destruction of war. These conditions are taxing to the utmost the capacity of the entire world in food production and our scientific inge-

nuity in distributing it to yield the greatest efficiency, both qualitatively and quantitatively. Many years of intensive agriculture and free flow of food to all parts of the world will be necessary if we are to extricate ourselves from this desperate situation. Scientific nutrition is contributing in a fundamental way to the solution of these problems.

Perusal of the voluminous literature in the field of nutrition during the war years discloses no curtailment in either volume or quality of investigation. The present edition attempts to record the new information and to integrate it with older material. For the sake of brevity and utility of the volume much has been omitted which might properly be included in a more comprehensive text on nutrition. These omissions, however, have been largely in the biochemical phase of the subject.

Change to another field of work has deprived me of the close association with Dr. Elmer L. Sevringhaus which I have enjoyed for so long, and also his co-authorship of this volume. He has continued, however, to provide valuable counsel in the preparation of the material for the present edition. I am also grateful to Dr. C. A. Elvehjem for the interest he has continued to take in this effort to present the facts of nutrition in a manner that will be of practical value to the physician upon whom falls the responsibility of disseminating accurate and dependable information and sound advice.

—EDGAR S. GORDON, M.D.

November 16, 1946

PREFACE TO THE SECOND EDITION

The period of two years since the first edition of this volume appeared has been an interesting one in the field of nutrition. Experimental work with laboratory animals has clarified a great many confusing details relative to some of the better known nutritional factors and has added several new factors. The vitamin B complex, perhaps contrary to expectations, has actually been somewhat simplified by the demonstration of some overlapping of biologic effects from certain of the components and a consequent merging of preexisting nutritional entities. From the standpoint of clinical nutrition, perhaps even more remarkable progress has been made as the unjustified overenthusiasm of clinicians for uncritical vitamin therapy has abated somewhat. There has been a significant trend in the direction of careful, critical, well controlled experimentation on human subjects for the purpose of observing the clinical manifestations of induced, single deficiency diseases, for measuring the balance between intake and output of single factors under controlled conditions and for determining the dietary requirements for each component necessary for the prevention and cure of abnormalities. This is obviously a healthy trend since it helps to establish human nutrition on a sound, quantitative basis com-

parable to that which is more easily attained for experimental animals.

Out of all these painstaking investigations have emerged several important concepts. First, so far as good nutrition is concerned, more that optimal amounts of vitamins are not needed, since tissue cells respond at an optimal rate, both anatomically and physiologically, to the proper concentrations of nutrients brought to them. Second, many chemical compounds with recognized nutritional significance have side actions which, under certain circumstances, may have therapeutic value unconnected with their vitamin activity. Third, vitamin deficiency diseases are characterized by biochemical changes and anatomic lesions which regularly appear in the order mentioned. Therapeutic response in these diseases follows the same sequence, and the anatomic lesions may persist for some time after recognition by biochemical means is impossible. Fourth, nearly all naturally occurring avitaminoses represent mixed deficiency states. It has been interesting and disturbing to find the clinical pictures of various induced, pure single deficiencies quite unlike the naturally occurring diseases. Fifth, there are important vitamin interrelationships that are only now beginning to be uncovered. Thus, the absorption, metabolism and excretion of one factor may be conditioned in part by the nutritional status of the organism relative to other (perhaps all other) nutrients.

There is no harm in setting up a series of postulates of this sort to be reexamined at intervals in the light

of new knowledge. It is quite possible that many or all of them will need alteration in the future, although the evidence for each one appears strong at present.

It is the continuing purpose of the authors to present the available facts of clinical nutrition in as concise and correct a form as possible, divested of as much fancy and unsubstantiated belief as can reasonably be eliminated. Unfortunately, in a rapidly changing field of this sort a great deal of uncertainty will continue to exist indefinitely, but the revision presented here has been brought completely up to date.

We have continued to enjoy the valuable counsel and friendly interest of Dr. C. A. Elvehjem and Dr. Marian S. Kimble, both of whom have been of the greatest help in preparing and correcting the manuscript. We are also grateful to a score of others among our colleagues who have rendered assistance in various ways.

—Edgar S. Gordon, M. D.
—Elmer L. Sevringhaus, M. D.

September 25, 1942

PREFACE TO THE FIRST EDITION

In this volume is presented a survey of the current information about nutrition organized for the sake of the clinician who wishes to understand the rea-

sons for specific steps before he prescribes diet therapy. For the sake of brevity, documentation of the argument has been omitted. This does not imply any lack of recognition of the contributions made by an uncounted group of authors to whom the medical profession and the human race stand in eternal debt. In this book there is not space to include specific menus for clinical dietetics. These will be found in the larger texts on dietotherapy, which are not to be replaced by such a volume as this. Limitations of size have also led to omission of tabulated data of food composition, save for the recent information on vitamins which is not easily found in book form elsewhere. As sources of ready reference for the composition of ordinary foods and beverages, the standard work has long been that by M. S. Rose, Laboratory Handbook for Dietetics (New York City: The Macmillan Company, 1932). Improvement in organization of material and inclusion of more recent data led to wide use of the late M. A. Bridges' Food and Beverage Analysis (Philadelphia: Lea & Febiger, 1935), most of which is incorporated in Dietetics for the Clinician by the same author. A useful, abbreviated table compiled by the late Mrs. D. S. Waller, is entitled Nutritive Value of Foods (Ann Arbor, Mich.: G. Wahr, 1939).

Special tables of the vitamin content of foods, prepared by Esther Peterson Daniel and Hazel E. Munsell, may be found in Vitamin Content of Foods, U. S. Dept. of Agri., Misc. Pub'n. no. 275 (Washington, D. C.: Government Printing Office, 1937), and

Milbank Memorial Fund Quarterly, October, 1940.

In presenting the current concepts and information about nutrition, we realize that new facts are being discovered so frequently that no book can be entirely up to date by the time it is read. Every effort has been made to include as much as possible of the recent work. This accounts for the frequent expressions of possibility and probability rather than certainty.

Throughout the work of preparing the manuscript, as in the clinical practice and research on which it is based, we have enjoyed the friendly and enthusiastic cooperation of many colleagues. It is a pleasure to acknowledge the assistance of Dr. Helen Parsons and the young women in her laboratory. The assistance of Mr. E. G. Kuenzi, pharmacist to the State of Wisconsin General Hospital, has been of great value in obtaining information about commercial preparations. The continuing counsel of Dr. C. A. Elvehjem has been invaluable. In the biochemical work, we have enjoyed the cooperation of Dr. Marian Stark Kimble, Chemist to the State of Wisconsin General Hospital and we are pleased to record our gratitude for criticism of the manuscript.

—-Edgar S. Gordon, M. D.
—Elmer L. Sevringhaus, M. D.

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WHAT IS A VITAMIN?

A vitamin may be defined as a specific chemical substance which is necessary in small amounts for the proper functioning of the complete organism and which must be obtained preformed from outside sources. Vitamins, like hormones, may in a sense be classified as catalysts, since relatively small amounts of active substance produce chemical changes of considerable magnitude. Perhaps the most important distinction between these two classes of vital biologic materials is their source. Hormones are produced within the organism from simpler compounds, by synthetic processes; vitamins cannot be synthesized because the organism does not possess the chemical mechanism for accomplishing that process. It is noteworthy, however, that some species of animals are able to build certain compounds which other species, for lack of this capacity, must obtain in the diet. Thus ascorbic acid, or vitamin C, is a necessary nutritional component for both man and the guinea-pig, whereas for the rat a deficiency of this factor does not exist, since it is able to supply its needs through endogenous synthesis. For this reason, ascorbic acid might be considered a vitamin for humans and guinea-pigs and a hormone for rats.

No general statement may be made to cover the

mode of action of vitamins. Their mechanisms vary widely, and each must necessarily be discussed separately. Several of the known factors have been found to act as prosthetic or active groups attached to a protein or other complicated molecule to form an enzyme or coenzyme. Such substances might be said to exert their actions through their respective enzymes. Indeed, it is highly probable that both hormones and vitamins produce their physiologic effects largely through the mechanism of enzyme action. In any event, the rôle of catalysis must be emphasized in this connection. The metabolic needs for each of these factors are so surprisingly small that their effects must necessarily result from their capacity to alter the rates of chemical reactions involved in metabolism.

The concept of deficiency disease is easy to grasp and is attractive to the physician engaged in practice. The reason for this may be that therapy is so easy and usually so satisfactory provided the missing components are available. It is immediately apparent that deficiencies may exist in all grades of severity, ranging from an almost total lack of a certain specific factor to a slight and relatively insignificant deficit of one or more such factors. The latter type is obviously the more common, but despite the frequency with which borderline or "subclinical" nutritional states are encountered, in almost no instance is it yet possible to evaluate with any appreciable degree of accuracy the resulting impairment of health. General clinical impressions have gradually arisen, and some serious attempts have been made to subject this aspect

of nutrition to careful study, but unfortunately our ideas concerning the consequences of borderline deficiency disease are still vague and unsatisfactory.

In addition, deficiency diseases may exist in either acute or chronic forms with all gradations between, and often acute forms are superimposed on the chronic. It is convenient to consider the development of deficiency states in four stages which, from the practical standpoint, merge imperceptibly and progressively. The first of these is a suboptimal intake of any one or several nutritional factors. This is soon followed by the second stage, with depletion of storage reserves which are always present with good nutrition. After a certain period the third stage appears, which may conveniently be termed a biochemical lesion since it is characterized by metabolic changes detectable by chemical investigation. Finally, and usually after prolonged depletion, the fourth stage—tissue changes—appears. The development of these tissue changes is gradual and their response to therapy equally slow, so that they are the last manifestation of the disease to disappear. For this reason measurable chemical changes in all accessible body fluids and intracellular chemical processes may be quickly restored to normal by the administration of adequate supplements of missing nutrients without correctly reflecting the continuing evidences of the deficiency state in the form of persisting lesions of the tissues which are restored to normal only after months or even years of good nutrition. The critical detail in this entire mechanism therefore appears to be the amounts of all necessary nutritional factors actu-

ally delivered to each tissue cell by the circulation. There is no evidence that a great excess will produce more rapid or more satisfactory amelioration of tissue abnormalities than will an optimal amount, the average magnitude of which has now become fairly well established in the form of the various "optimal daily requirements." Good students of nutrition, however, are recommending progressively larger dosages in the therapy of long-standing deficiency states in the hope that a great abundance of all necessary factors will hasten the repair of damaged tissue cells.

A new mechanism in the production of deficiency states has gradually been recognized. It concerns the occurrence in foods of "antivitamin" substances. These are chemical compounds, closely related in structure to the various known vitamins, which derive their antagonistic action from their ability to replace the vitamin in certain, but not all, chemical reactions. Their practical significance in causing deficiency states is unknown but is probably inconsequential. For this reason it does not seem worth while to consider them in detail in a discussion of this kind.

Clinical conditions presenting a lack of a single dietary constituent are rare. More often, multiple deficiency states are encountered. Appreciation of this circumstance has been derived from the realization that many of the conditions originally ascribed to lack of a single factor, such as beriberi and pellagra, are somewhat more complex. This was established only after isolation and synthesis of various vitamin factors in pure form made them available for experimen-

tal work. Therapy for deficiency disease therefore usually involves the use of more than a single constituent, as the subsequent discussion is intended to show.

Because an adequate supply of vitamins will cure the manifestations of deficiency, it does not necessarily follow that a larger supply will produce additional benefits. Indeed, this is by no means the case. Generally speaking, the scientifically justified rationale of vitamin therapy must be considered to be the restoration of depleted reserves of essential nutritional factors and their continued supply in optimal amounts to all tissue cells for indefinite periods. When the storage capacity has been filled, even though prompt excretion of excess materials can be readily demonstrated, there remains a sound basis for further administration of a reasonable excess of these nutrients for prolonged periods, because of the slow reversibility or the near-irreversibility of tissue changes that result from long-standing deficiency states.

There continue to appear in the scientific literature a large number of reports indicating therapeutic usefulness of pure vitamin preparations in dosages so high as to preclude the possibility of effects based on simple improvement of nutrition. They raise the question of a possible additional physiologic action of some of these compounds, an action which might best be termed pharmacologic since it is comparable to that of other drugs. Many such effects in human beings are probably psychic and therefore difficult to evaluate. Careful, well controlled investigations in this field are

rare, but the possibility of a druglike action is too real to be easily dismissed. Fortunately, vitamins in reasonable dosage usually have no toxic effects, so that no harm is done by their indiscriminate use, and it is often necessary to establish a diagnosis by means of a therapeutic trial. It is easy to exaggerate the therapeutic usefulness of these materials and to expect dramatic results from their administration. Furthermore, it is easy to be carried away by the beautiful effects obtained under the proper circumstances, with the ultimate result of prescribing ridiculous and unreasonable dosages.

Therefore there is an urgent need for objective, chemical laboratory methods by which specific vitamin deficiencies may be recognized, regardless of the severity of the condition. Since the clinical manifestations in mild cases are always vague, such laboratory methods may be considered a necessity for the intelligent and alert clinician, to replace the uncertainty of guesswork and therapeutic trial. The technics must necessarily be simple enough to be adaptable to most hospital laboratories, and satisfactory criteria of deficiency disease must be established for each factor. There is every reason to hope that at some future time means of determining vitamin A, ascorbic acid or thiamine in blood or urine will be as readily available and useful to the clinician as are those for determining blood sugar, nonprotein nitrogen and urinary glucose at present. We are still rather far from that goal.

Vitamins, like hormones, need to be administered intelligently according to requirements. This imme-

diately places therapy on a quantitative basis and indicates the need for accurately standardized commercial preparations. The establishment of vitamin dosages on a weight basis has gradually superseded the unit system as pure crystalline preparations have become available to replace impure concentrates whose potencies are necessarily estimated by animal assay. It might eventually be possible to provide human beings with complete daily nutritional requirements in pure form dispensed in bottles and prescribed on an accurate quantitative basis according to the metabolic needs of the individual, but such a goal is as undesirable as it is fantastic, since food remains the best source of nutritional factors. The use of complete, well balanced diets should be encouraged as the best prophylaxis against deficiency disease. With the objective of insuring adequate diets to the entire population, the national movement for enrichment of staple foods sponsored by the Federal government is thoroughly sound and deserves universal support. Under ideal conditions, such a program combined with widespread education in nutrition should make the use of additional vitamin supplements unnecessary, and the pure vitamin preparations now sold in great abundance across drug-store counters to millions of people for self-medication should be reserved for use, under medical supervision, in the treatment of nutritional deficiency disease.

VITAMIN A

Although the disease xerophthalmia has been known for many centuries, its nature remained obscure for about a decade after the concept of deficiency disease was first stated by Grijns. The missing factor in the production of this condition was actually discovered by McCollum and Davis in 1914 and was named by them fat-soluble A because of its occurrence in butter, cream and cod liver oil. This same designation served also to distinguish it from the water-soluble B whose existence had been recognized about three years earlier. Thus our knowledge of even the existence of vitamins covers a total period of approximately a third of a century during which time they have been subjected to constant investigation and many of the problems concerning their nature and action have been satisfactorily settled.

Vitamin A, which has as yet no other official designation, is a fat-soluble, unsaturated, nitrogen-free alcohol with a molecular weight of 294. Its structure is represented by the formula shown in Figure 1, and that of its precursor in Nature, beta carotene, in Figure 2. Vitamin A is unstable and readily destroyed by oxidation when heated in the presence of air. It is not destroyed, however, by anaerobic heating or by saponification of the fats in which it occurs. The
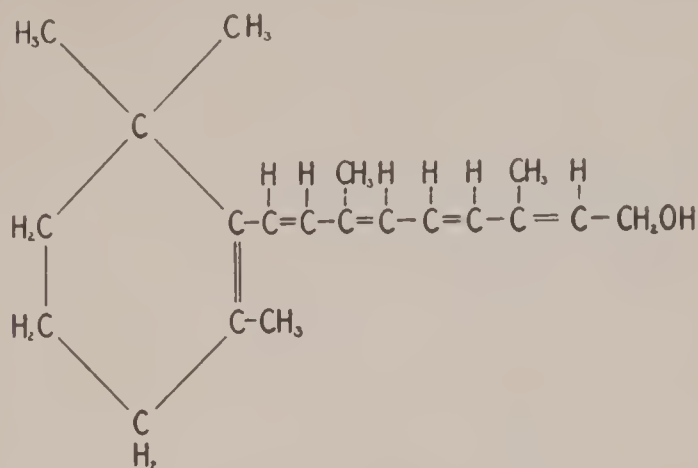
Fig. 1.—Vitamin A.

alcohol has been found to be more easily destroyed than the esters. Since it occurs in esterified form in blood and in the storage depots, it is quite resistant to destruction under these conditions. It is thought that various mechanisms exist in biologic systems which provide protection for vitamin A against oxidation, one of which may be vitamin E. Synthesis of vitamin A has finally been accomplished after many
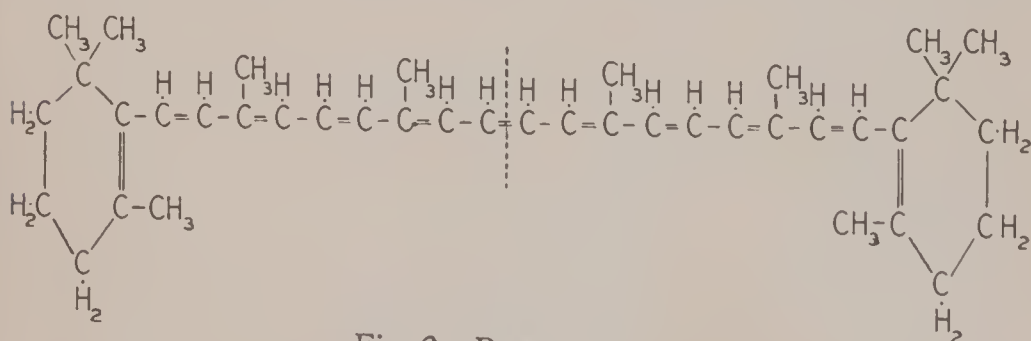
Fig. 2.—Beta carotene.

years of unsuccessful attempts. The compound has a biologic potency of only one-tenth to one-thirtieth that of pure crystals derived from natural sources, but is 50-100 times as potent as ordinary cod liver oil.

Carotene is a member of a series of compounds

called carotenoids which are abundant in Nature. The chemical structures of about 30 of these substances are now known. Of these, only four have vitamin A activity. Familiar carotenoid pigments are the red coloring matter of tomatoes, the red pigment of lobsters, the yellow of buttercups and dandelions, the red of paprika and pimento and the yellow of corpus luteum. The four substances showing vitamin activity are known as alpha carotene, beta carotene, gamma carotene and cryptoxanthin. Of these, beta carotene is capable of being split by hydrolysis into two molecules of vitamin A; the others yield only one molecule each. Whereas carotene has an intense yellow color, pure vitamin A is colorless.

Pure beta carotene serves as the international vitamin A standard, 1 I. U. representing the growth-promoting activity in rats of 0.0006 mg. of the standard beta carotene. The validity of this method of standardization may be questioned in view of the poor intestinal absorption of pure beta carotene. So far as is known, all vertebrates must derive their supplies of carotenoids from plants, since none of these animals has the power to synthesize the pigment. This is not true of many other vitamins, and this observation provides a basis for the greater applicability of results of animal experiments concerned with vitamin A to problems in human nutrition.

Most animals, including man, possess the capacity for storage of large amounts of vitamin A. This permits survival through periods of inadequate intake without the appearance of any deficiency manifesta-

tions. Approximately 90-95 per cent of the vitamin A reserves in rabbits and in rats is found in the liver, which is probably also true in man. This storage material for the most part is not free vitamin but in the form of esters (compounds of alcohols and acids), the palmitate being the most prominent. The reserve supply in the human liver under ordinary good nutritional conditions has been estimated as 10-20 mg. per 100 Gm. tissue.

Toxicity of carotenoid compounds has been studied, but there is wide divergence in the conclusions. Xanthosis cutis, or yellow coloring of the skin, is a common finding with high intake of carotene. The pigment tends to appear first around the nose, ears and palms of the hands. It never colors the scleras and therefore can usually be distinguished from true icterus. This condition is always accompanied by high carotenemia, giving the blood serum an orange-yellow tint which can be chemically distinguished from the golden color of bilirubin by extraction of the serum with petroleum-ether. Carotene immediately passes into the solvent, while bile pigments remain in the serum.

Excessively high doses of carotene or vitamin A (1,000,000 I. U. or more) may cause some anorexia and even nausea, but the effect is transient and has not been proved to be due to the vitamin per se. A variety of serious manifestations, and even death, has been reported in experimental animals. These changes consist of roughening of the skin, rarefaction of bones, alopecia and profuse hemorrhage. In rats, from 15,000

to 40,000 units daily of vitamin A will produce this result. The hemorrhage is due to a marked diminution of prothrombin content of the blood, which is preventable or curable by the administration of vitamin K in small doses. A similar syndrome has been reported in human subjects. In these cases dosage was extremely high (more than 1,000,000 units daily); all cases were in children. From a practical standpoint, the danger of hypervitaminosis A is very slight if reasonable dosages are used.

Physiology and Pathology

Both vitamin A and carotene are absorbed from the gastro-intestinal tract to a large extent in the chyle. Careful studies have demonstrated almost quantitative recovery of vitamin A with poor absorption of carotene. Both substances gain access to the blood stream chiefly by way of the lymphatics and the thoracic duct. Intestinal absorption of the carotenoid pigments is affected by many factors discussed below.

The biologic function of vitamin A is apparently very complex, since it seems to be an essential factor for the physiologic integrity of many organs. In general, however, it may be considered chiefly as a regulator of the growth and activity of epithelial tissues. A deficiency produces atrophy of the epithelium, followed by a proliferation of the basal cell layer, which then differentiates into stratified squamous, heavily keratinized epithelium, regardless of the type of tissue originally present. This general process is known as keratinizing metaplasia and was familiar to patholo-

gists for many years before its relationship to avi-taminosis was recognized. By means of this process, it is common in severe vitamin A deficiency to find areas of stratified squamous keratinized epithelium scattered through the transitional epithelium of the genito-urinary tract, the pseudostratified epithelium of the respiratory tract or the secreting columnar epithelium of the gastro-intestinal tract and ducts and acinar tissue of secretory glands of various types (salivary, pancreas, uterus, etc.). In the eye, the earliest manifestations involve metaplasia of the cornea and conjunctiva, with some changes also in the lacrimal glands and ducts. In severe cases necrosis and ulceration of the cornea may follow, augmented by the failure of lacrimal secretion, from which the disease xerophthalmia derives its name. The resulting keratomalacia regularly produces blindness unless the process is stopped before the stage of ulceration.

In the skin, a dryness and roughness in the early stages is followed by a papular eruption caused by hyperkeratosis of the hair follicles. Atrophy of the sweat and sebaceous glands with keratinizing metaplasia of the ducts results in a dry skin. There is often a generalized increase in the melanin pigment. These changes are usually first seen on the lateral aspects of the thighs, followed in order by the forearms, extensor surfaces of the legs, shoulders, abdomen, back, buttocks and neck. They are easily studied by means of a small biopsy specimen, as the photomicrographs (Figs. 3 and 4) show.

Vitamin A deficiency probably ranks first in importance among avitaminoses as the cause of dental difficulties, particularly when this occurs in childhood during the period of formation of the enamel organ. Absent or defective enamel and dentin formation have been shown to be consequences of vitamin A deficiency in infants as well as in experimental animals. The defective structure so produced may account for dental caries in later life.

A wide variety of central nervous system lesions has been reported as a result of vitamin A deficiency in experimental animals of many species, but there have been no clinical reports of a similar type. More attention should probably be paid to this possibility.

Gastro-intestinal and genito-urinary lesions are usually not of great clinical importance, with the possible exception of kidney stones, which, although suspected of being associated with this specific avitaminosis, have not been satisfactorily proved to accompany the uncomplicated deficiency. Atrophy of the testes has also been reported in humans.

Of perhaps greatest interest at present is the rôle which vitamin A normally plays in the visual cycle through its participation in the synthesis of visual purple by the retina. Upon this aspect of eye physiology depends the commonest and most easily recognized manifestation of A avitaminosis, namely, night blindness or nyctalopia, also known as hemeralopia. The mechanism by which vitamin A enters the visual cycle is best illustrated by the diagram shown in Figure 5. Vitamin A is thought to combine in the
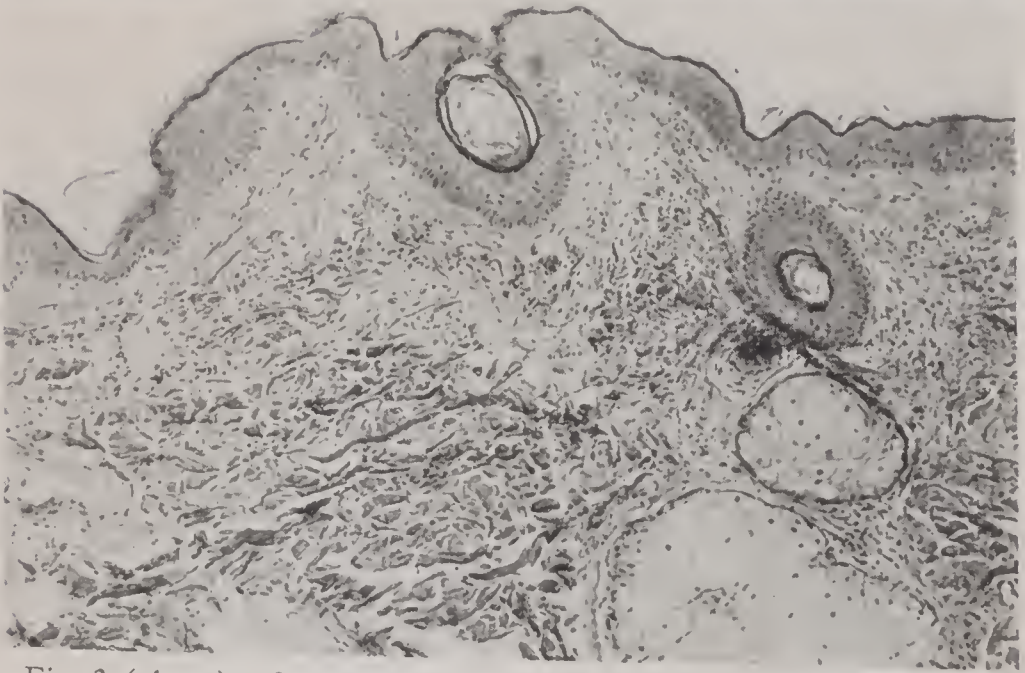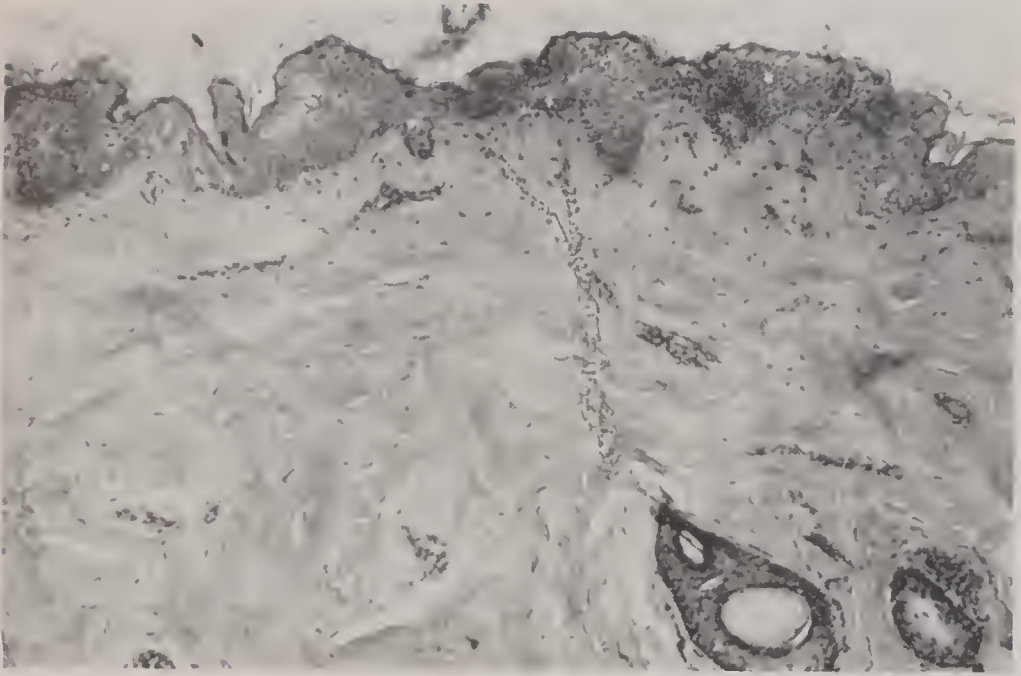
Fig. 3 (above).—Section of skin taken from patient with severe vitamin A deficiency; marked hyperkeratosis, vesiculation of many cells in prickle cell layer and dilated, engorged capillaries. Atrophy of hair follicles and sebaceous glands. (This and Figure 4 reproduced by courtesy of Dr. Hamilton Montgomery, Mayo Clinic.)

Fig. 4 (below).—Three weeks after resumption of normal diet; disappearance of all manifestations of deficiency except plugging of hair follicles by hyperkeratotic débris.

dark with a protein, possibly in the presence of phosphoric acid, to form the pigment rhodopsin, or visual purple. In the light, bleaching occurs with a decomposition of rhodopsin into retinene and a protein. Retinene is a golden-yellow lipid material, which on further exposure to light becomes visual white, which is not a carotenoid substance. Vitamin A is present
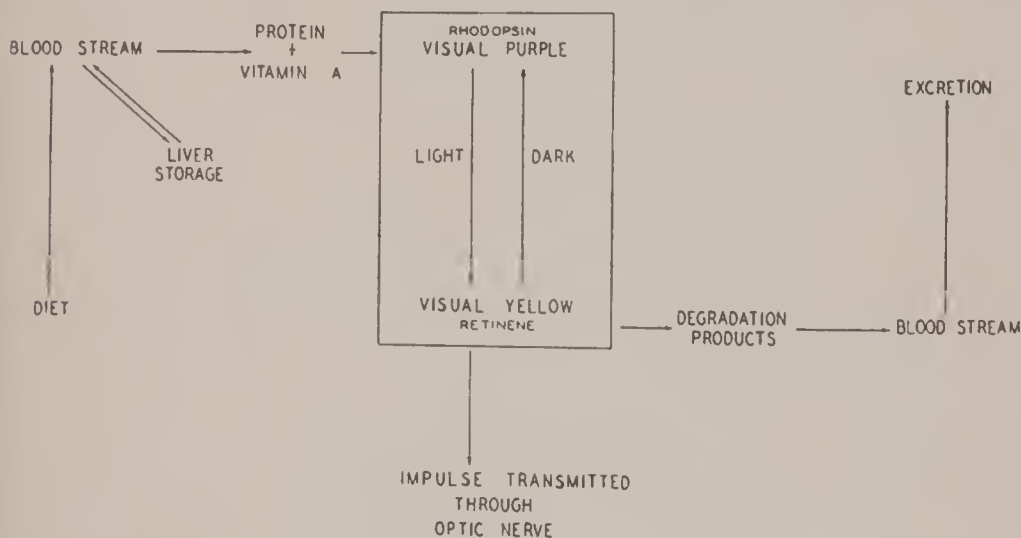
Fig. 5.—Diagram of visual cycle.

in the retina, and synthesis of rhodopsin does not take place in the absence of retinal epithelium. This synthesis is presumably an enzyme reaction, and there is abundant evidence that the vitamin A supply is not the only limiting factor. It is quite possible that riboflavin, ascorbic acid and probably other substances are also necessary. Although this cycle is remarkably efficient, owing to the constant resynthesis in the dark of rhodopsin from retinene and protein, nevertheless there is always some loss of degradation products which necessitates a constant new supply of vitamin A. This is brought to the retina by the circulating

blood, which may derive its supply from immediate intake, or may draw on the reserve store of the body, which is located chiefly in the liver.

Because the visual purple mechanism is concerned chiefly with vision in dim light, it is apparent that the unavailability of any single component in the chain of synthesis will result in impairment of the capacity to see in dim light to a degree that can be measured by an appropriate technic. Thus, the efficiency of adaptation from dark to light in A avitaminosis is definitely impaired. Various adaptometers, including the widely used biophotometer, were devised to measure the rate of this reaction by exposing the subject's eyes to a standard bright light for a measured period of time, after which the visual threshold is measured by determining the minimum amount of illumination necessary for the subject to perceive a lighted figure in a dark field. Normal standards have been set up, which may be used for comparison to distinguish the various degrees of deficiency in adaptation.

Numerous variations and improvements on the original biophotometer have been made in the hope of eliminating various objections raised concerning the validity of the conclusions to be drawn from such measurements. Space does not permit a review of the extensive literature on this subject, despite its importance as a criterion of clinical avitaminosis. Most investigators agree, however, that a reduction in the capacity for dark adaptation is a fairly constant manifestation of vitamin A deficiency, but the speed of its appearance during depletion is a matter of consid-

erable argument. As a matter of fact, there is the widest possible disagreement as to the reliability of these measurements in detecting early avitaminosis A, the incidence of that condition in the general population and the accuracy of any of the instruments now in use for measuring dark adaptation. For these reasons, specific recommendations concerning the biophotometer are difficult. The Birch-Hirschfeld photometer as modified by Jeans, Blanchard and Zentmire and named the biophotometer is the most common form of the instrument in use at present. It is probable that this apparatus measures in a qualitative and possibly in a roughly quantitative manner wide variations in dark adaptation, giving thereby, if other factors are controlled, an estimation of the vitamin A nutrition of the subject or at least his efficiency in performance of a process in which vitamin A is an important limiting factor. Whether borderline states of avitaminosis or small increments of change in performance are reliably detected cannot be positively concluded at present. Certainly there are many factors, some of them subjective, which seem to influence the results erratically. Refractive errors, particularly those of large magnitude, and retinal conditions such as hemorrhages and exudates will clearly invalidate the conclusions based on such an indirect test. Another factor of importance is the difference in adaptation which is known to exist between the macular area and the remaining portions of the retina, since scotopic or dark-adapted vision is thought to depend almost entirely on the rods, while

the cones are concerned with perception of color and other visual functions which depend on light of high intensity. Necessity for control of the pupil size has also been appreciated, and some of the newer forms of adaptometer take this factor into consideration. The subjective elements of cooperation and training are of the greatest significance in obtaining reliable results. Repeated tests on the same subject tend to produce a certain facility in performance which is not proportional to any true improvement in efficiency of adaptation. Vitamin A requirements of a single individual may deviate from the average requirements of large groups arrived at by statistical analysis of data.

The Hecht adaptometer is a newer and probably a more reliable instrument than the biophotometer, but it is more complex. The technic recommended for its use is more time-consuming, and extensive clinical work through its use has not been reported. It may therefore be concluded that some degree of caution is necessary in the interpretation of results of methods which employ the efficiency of dark adaptation as a diagnostic index of vitamin A subnutrition. This is somewhat regrettable, since this method appeared at first to offer a simple, easy, dependable diagnostic method within reach of all clinical groups.

Owing probably to the uncertainty of this method, the use of adaptometers of all types for general clinical purposes has diminished perceptibly in the past few years, and increased attention is being focused on chemical criteria. It must be recognized, however, that blood vitamin levels are sensitive chiefly to acute

changes and measure fluctuations in dietary intake and absorption quite adequately. They are relatively of much less value in chronic marginal deficiency states. This statement is perhaps less true for vitamin A than for the water-soluble vitamins, since rather prolonged periods of depletion have been found necessary to produce significant, sustained depression of the blood vitamin A level. Fluctuations in the dietary intake of carotene, on the other hand, are much more accurately reflected by blood analysis, probably because of the insignificant storage of the provitamin.

Changes in the scleras and conjunctivas resulting from avitaminosis A were described by Kruse and since then have been subjected to the examination and criticism of clinical investigators. As might be anticipated, there is a wide variance of opinion as to the validity of these observations. The lesions consist of increased vascularity of the conjunctivas, keratinization and piling up of epithelial cells to form the lesions heretofore referred to as Bitot's spots and xerosis conjunctivae. It is even possible that pinguecula and pterygium are far advanced stages of this same process. Kruse believes that these lesions represent the earliest detectable changes in avitaminosis A, even preceding failure of dark adaptation. His position has been challenged, and it is not possible to settle the matter at present. Of particular interest and importance is his demonstration of microscopic structural changes which respond slowly to adequate supplies of vitamin A. They represent chronic hypovitaminosis of variable degree and must be expected to persist

long after improved nutrition has restored all chemical measurements to normal.

The etiology of various skin lesions has also been ascribed to hypovitaminosis A of a chronic type, for which massive doses (100,000 I. U. daily) have been prescribed over periods of several years. Among these are follicular hyperkeratosis, facial keratosis, pityriasis rubra pilaris, benign dyskeratosis, lichen planopilaris, ichthyosis, acne vulgaris, corns and callosities. The histologic common denominator of all these lesions is a local increase in cornification which may be a response to local diminution of vitamin A available to individual tissue cells, due to any of several apparently unrelated causes such as pressure ischemia, slowed circulation, low vitamin A level in the blood, local destruction of the vitamin, or a combination of these. In some of these clinical conditions adequate laboratory evidence indicates the relationship to vitamin A; in others the association is conjectural and based on inadequate empiric data. Sullivan and Evans[1] have created still more uncertainty about these relationships by showing that in animals the "typical" avitaminosis A lesions are often caused by multiple deficiencies, usually involving the B complex group.

The metabolism of vitamin A and carotene during pregnancy and lactation is a relatively unexplored field. It is known, however, that the blood vitamin A level of the infant at the time of birth is usually in the range of 50 per cent of that of the mother and the level of carotene roughly one-tenth that of the

[1] Sullivan, M., and Evans, V. J.: J. Nutrition, 25:319, 1943.

mother, an observation which suggests that the placenta constitutes an effective barrier to the passage of both the vitamin and its precursor. This belief is further substantiated by the failure of response in the infant's blood when large vitamin A supplements are administered to the mother during the weeks im-
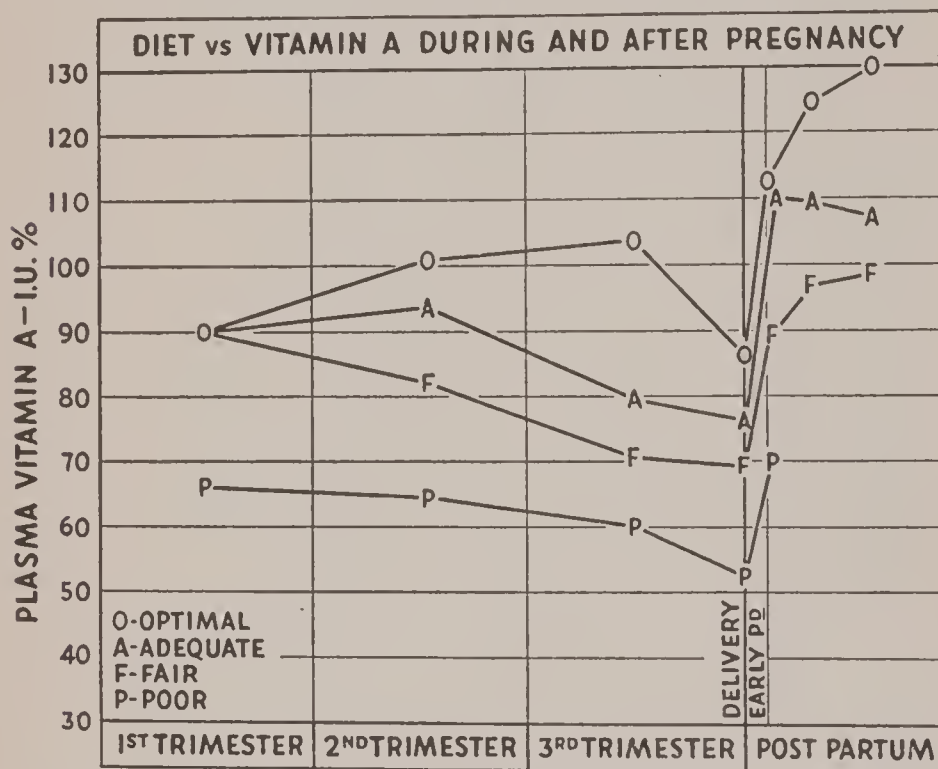
Fig. 6A.—Mean plasma vitamin A values of patients grouped according to diet. Gestational decrease occurs in all, but degree varies with time and diet. All show striking mobilization of vitamin A into blood post partum. (Figure 6 from C. J. Lund: J.A.M.A., 128:344, 1945; with permission.)

mediately preceding parturition. It is equally interesting, however, that abnormally low blood levels in the mother resulting from poor diet are not accompanied by corresponding depression of the infant's blood level, the latter regularly maintaining a vitamin A content which may at times exceed that of the mother. Maternal plasma levels almost invariably de-

cline as pregnancy progresses, reaching their lowest levels immediately before parturition. The magnitude of this decline roughly parallels the vitamin A intake in the diet. Within 12-24 hours after delivery the plasma level rises sharply, which suggests that signifi-
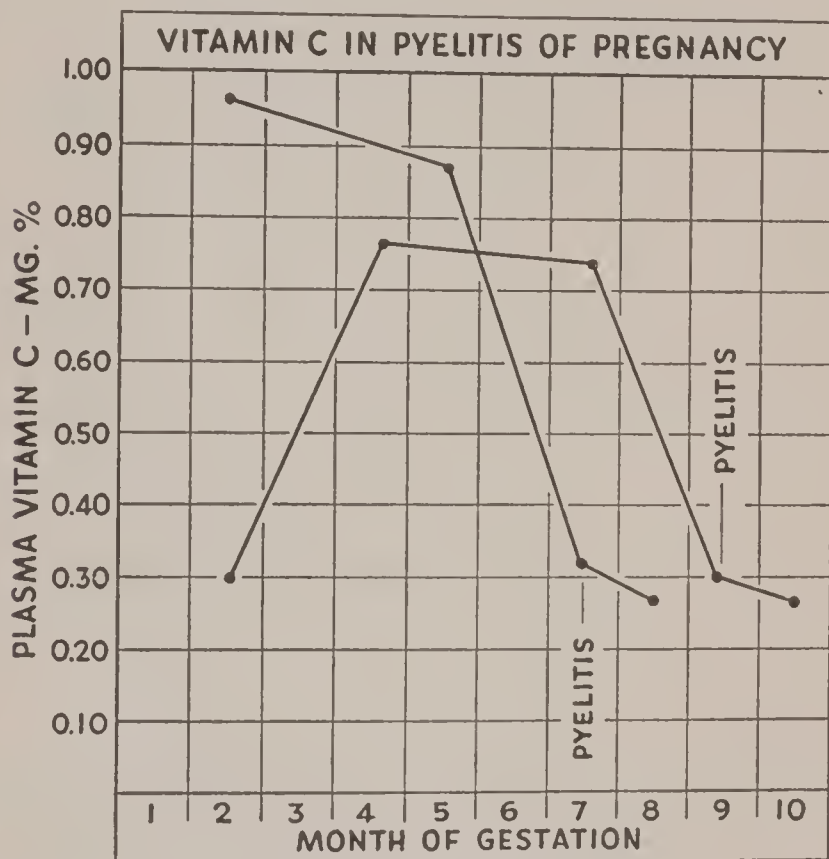
Fig. 6B.—Two cases showing rapid depletion of vitamin C in pyelitis of pregnancy.

cant amounts stored during the pregnancy are mobilized at the time of delivery to provide for lactation. Figure 6A, based on data of Lund,[2] illustrates such changes in relation to the adequacy of the diet. These findings suggest that most diets during pregnancy are inadequate in vitamin A, and Lund recommends supple-

[2] Lund, C. J.: J. A. M. A., 128:344, 1945.

ments of 5,000 units daily during the second trimester
and 10,000 units daily during the third trimester.

After parturition, under normal conditions the in-
fant is assured of adequate vitamin A intake by the
high content of colostrum which, in the human being,
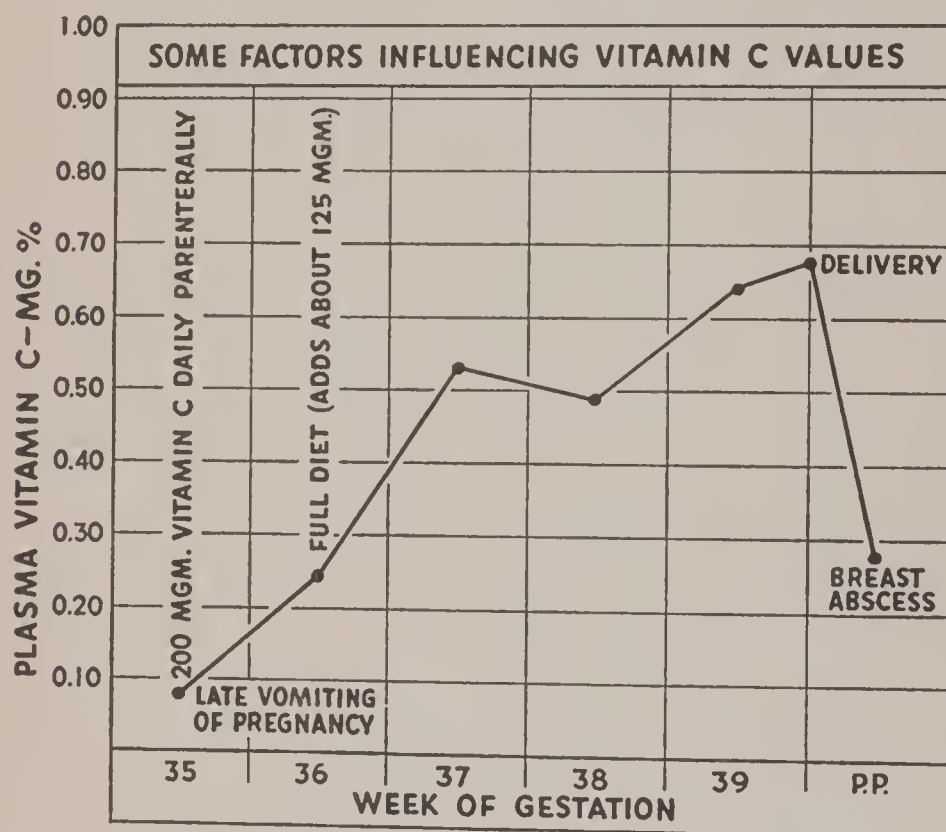
Fig. 6C.—Low plasma vitamin C levels with late vomiting of pregnancy.
Fairly large amounts (325 mg. daily) slowly elevated plasma level but
failed to maintain that level after acute infection.

may be two to three times that of the milk which fol-
lows. (The vitamin A content of early human milk
varies from 170 to 400 I. U. per liter and is roughly
one and a half to four times its concentration in cow's
milk.) Studies in normal lactating women have shown
that the vitamin A content of breast milk tends to
diminish progressively as lactation proceeds. It is also

known that at any single pumping there is an increase in content of both vitamin A and carotene, so that the highest concentration occurs in the last milk to be removed from the breast.

Sources and Requirements

The best dietary sources of vitamin A and its provitamin are butter, cream, egg yolk, fish liver oils and green leafy vegetables. The actual values for a number of common foods are given in Table 1.

The minimum daily requirement of vitamin A for a normal adult is probably about 2,000 I. U., or 5,000 I. U. of beta carotene. This is certainly not enough to provide for more than the minimal amount to prevent the appearance of measurable deficiency. A daily intake of 2,000 to 4,000 I. U. is recommended for adults by the Commission for the Study of Nutrition of the League of Nations. The National Research Council recommends 5,000 I. U. daily. Growing children probably should receive 6,000-8,000 units daily. This amount can be supplied by the inclusion in the diet of 1 qt. of milk, one egg, servings of leafy green vegetables, butter and 1 teaspoonful of cod liver oil daily. New-born infants particularly need a large intake of vitamin A because their liver reserves are only about one-twentieth those of adults per unit of weight. Since this vitamin must come from the mother, it is equally important that her intake be adequate, certainly not below 6,000 I. U. in 24 hours and preferably above 8,000 I. U. If the infant is artificially fed, this amount must supplement the formula.

Certain physiologic factors have been found to affect the utilization of vitamin A in the diet. The fat content of the diet has an important effect on the

TABLE 1.—Vitamin A Content of Foods*

	I. U. per 100 Gm.
Apricots	2,790
Asparagus	1,000
Bananas	430
Beans, green	630
Beef	Neg.
Beet greens	6,700
Broccoli	3,500
Butter	3,300
Cantaloupes	3,420
Carrots	12,000
Celery, green	1,050
Cheese, cream	2,210
Corn, fresh yellow	390
Corn, canned yellow	200
Cream, 20%	830
Dandelion greens	13,650
Eggs	1,140
Lettuce	540
Liver	19,200
Milk, whole	160
Milk, skim	Trace
Peas, green	680
Peaches, yellow	880
Peaches, dried	3,250
Peppers, green	630
Prunes, dried	1,890
Spinach	9,420
Squash	4,950
Sweet potatoes, yellow	7,700
Tomatoes, ripe	1,100
Turnip greens	9,540

* These figures are from Tables of Food Composition prepared by the Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, in co-operation with the National Research Council, Miscellaneous Publication no. 572 (1945). Nutritive values are given for foods as brought into the house for consumption; no account has been taken of losses of food value that may occur in preparation of meals.

absorption of both vitamin A and carotene from the intestine. In human subjects on fat-free diets, only half of the dietary carotene is absorbed as compared to an 80 to 90 per cent absorption when a moderate

amount of fat is present. Recent observations indicate that vitamin A is almost quantitatively absorbed from the intestinal tract when given in moderate dosage. With intakes above 75,000 I. U. daily, however, fecal excretion rises sharply. Under the same conditions, carotene is only about 40 per cent as effective as the vitamin because of poor absorption. Once in the blood and tissues, its potency is apparently identical to that of vitamin A. Bile, which is essential for normal fat digestion, is apparently necessary for the absorption both of carotene and of vitamin A, but it is of much greater importance for the former. This fact has certain obvious implications for the management of diets of individuals with disease of the biliary system with obstruction.

The use of mineral oil in large amounts may interfere to a variable extent with the absorption of carotene and vitamin A, although the difference in behavior between the two compounds under these circumstances is not clear. It seems wise, however, to arrange the time of administration of mineral oil so that it does not coincide with the postprandial absorption periods, and the total dosage of oil should be reduced to a minimum consistent with the desired therapeutic effect.

A metabolic anomaly has been reported in both hypothyroidism and diabetes mellitus characterized by a failure of the normal capacity for conversion of carotene into vitamin A. Recent studies, however, have cast considerable doubt on the validity of these observations relative to diabetes mellitus. They re-

veal, instead, no characteristic pattern in the carotene-vitamin A relationship, and no reason to doubt adequate conversion of the provitamin. The higher incidence of xanthosis cutis in diabetics has therefore not been adequately explained. The thyroid-vitamin A relationship is still not clear, although there is evidence to indicate that thyroid extract facilitates the tissue utilization of the vitamin. Evidence of a biologic antagonism between the two substances, however, is not convincing.

Special mention should be made of the importance of liver disease in the metabolism of vitamin A and carotene. Since this organ represents the chief site of storage as well as the probable site for the conversion of carotene to vitamin A, it appears only reasonable that extensive parenchymal damage will interfere with both of these, as well as all other functions of the liver. In such individuals, the vitamin A nutrition may be maintained at a reasonably good level by the constant use of preparations of vitamin A, but the capacity for storage is reduced in proportion to the extent of the liver disease, so that a deficiency quickly supervenes if the external supply fails.

In addition to the factors cited, there are undoubtedly a great many more about which we know nothing at present. The metabolism of this vitamin and its precursors is very complicated, so that we must rely on future work to clarify the utilization of these compounds.

In the clinical evaluation of the status of vitamin

A nutrition the biophotometer or other adaptometer has unquestionably been of distinct value. Its limitations must be appreciated and the results interpreted on that basis until a more satisfactory means is devised for the measurement of the speed of dark adaptation. Even when such technics have been developed, they will still measure only the efficiency of the visual cycle, which does not necessarily reflect either the reserves or the total metabolism of vitamin A in the organism as a whole.

In the meantime, the determination of the levels of both vitamin A and carotene in the blood has become helpful, since good methods have been developed. Most of them involve the quantitative use of the Carr-Price reaction by which a blue color develops when antimony trichloride is added to a solution containing a carotenoid pigment. Numerous adaptations of the original method have been worked out with a view to improving its simplicity and accuracy. The best of these derive their accuracy from the use of a suitable photo-electric colorimeter for estimation of the color intensity. Using one such reliable method, the normal values for vitamin A in blood have averaged 96 I. U. for women and 126 I. U. per 100 cc. of blood for men. Another laboratory using a similar method but with certain modifications has reported average levels of 212 I. U. for men and 182 I. U. for women. Thus the need for uniformity in chemical methods is apparent. Since a postprandial rise does not occur under ordinary dietary conditions, it is not necessary that the blood be taken under fast-

ing conditions. This failure of the blood level to change is due probably to two factors: (1) a large part of the vitamin A potency of an average meal is due to carotene which must be chemically split before it can be measured as vitamin A, and (2) the simultaneous absorption of other substances slows down the transfer of the vitamin through the intestinal mucosa. Following large doses of vitamin A concentrate (30,000-250,000 I. U.), it is common to find a marked rise in the blood level, reaching a peak in six to seven hours. It must be emphasized that blood values for any factor which is capable of being stored by the body in large amounts do not necessarily represent the state of depletion of these stores but reflect rather the balance between storage and utilization by the peripheral tissues. Indeed, animal experiments have shown that from 50-80 units of vitamin A per kilogram of body weight is necessary in the diet each day before any appreciable liver storage takes place. For these reasons the blood levels must be interpreted with some reservations. They also provide one possible explanation for the often noted lack of correlation between the blood vitamin A content and the biophotometer performance, since the latter is at least a rough index of the utilization of this substance by one highly specialized tissue. In addition, in the rat it appears that the liver stores must be nearly completely depleted before hemeralopia develops. Experience with the clinical use of a dependable blood method shows it to be of definite value and probably more reliable as a criterion of nutritional status than the biophotometer.
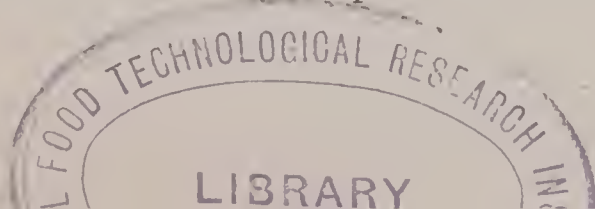
Ruch, Brunsting and Osterberg[3] developed a vitamin A tolerance test to assist in the diagnosis of deficiency states, in the hope of eliminating some of the errors of simple blood analysis. This technic involves oral administration of 7,500 I. U. of vitamin A after 12 hours of fasting. Blood is then drawn at two, four, six, nine, 12 and 24 hours to provide a blood concentration curve which represents the balance between absorption and storage. Because storage is increased in patients with depleted reserves, a sharp differentiation between normal and deficient subjects is possible, with the latter group consistently having a curve of lower concentration. Such a test probably could be further simplified to provide a valuable diagnostic method in routine nutrition studies.

The frequency of occurrence of infections of all types in severe vitamin A deficiency has made the therapeutic use of preparations of this vitamin popular in the treatment of colds and minor infections. Critical analysis of this point has been carried out from a variety of aspects, many of which seem to support the impression that even mild grades of avitaminosis are responsible for increased susceptibility to common colds and other infections. Since this is a difficult problem to investigate, many of the data are poorly controlled and unreliable, but statistics that are available seem to indicate that the duration of colds in subjects receiving vitamin A is less

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3 Ruch, D. M.; Brunsting, L. A., and Osterberg, A. E.: Proc. Staff. Meet., Mayo Clin., 21:209, 1946.

than that in control groups. However, it seems safe
to conclude that although a good general nutritional
status is undeniably a predisposing factor to good
health, there is no justifiable basis for recognizing
vitamin A as specifically the "anti-infective vitamin."
Recent well controlled studies on human subjects have
failed to reveal any relationship between known quan-
titative immunologic reactions and prolonged periods
of vitamin A depletion. These results seem to con-
tradict rather wide clinical and lay experience, but
the fact remains that a correlation between suscepti-
bility to colds and infections and avitaminosis A has
not yet been experimentally demonstrated. The
chronicity of the nutritional defect may provide the
answer. In addition, animal experiments leave little
doubt that this lowered resistance is more closely corre-
lated with inanition and the poor general nutritional
status which regularly coexists with avitaminosis A
than with the specific lack of that factor in the diet.
Consequently, nutritional therapy for individuals who
are abnormally susceptible to colds should consist of
general measures in which may correctly be included
sufficient cod liver oil, haliver oil or other vitamin A
concentrate sufficient to provide a daily intake of twice
the individual's daily requirement, namely, 5,000-10,000
I. U. Again it should be emphasized that no especial
benefit should be anticipated unless a deficiency in this
factor bears an etiologic relationship to the infections.

The occurrence of night blindness is common in the
population at large, although accurate statistics are

not available. Fortunately, it is present to only a limited degree in the greater proportion of individuals involved. Chief complaints are difficulty in acuity of vision and easy eye fatigue after the sun goes down, under conditions of artificial illumination. Quick accommodation to darkness, as in entering a moving picture theater, is impossible. Most serious of all is the temporary blindness in automobile drivers which follows the glare of headlights on the road at night. This difficulty has been shown to be responsible for an appreciable number of night highway accidents. Visual disturbances of these types are often attributed to refractive errors or other eye conditions, but will usually respond promptly to proper dietary measures.

Therapy of Vitamin A Deficiency

The treatment of night blindness with vitamin A supplements is rational and productive of excellent results except in instances in which that complaint is due to a cause other than avitaminosis. It should again be recalled that vitamin A is only one of the constituents of visual purple and that derangement of the visual cycle may occur as a result of other abnormalities. Administration of vitamin A supplements up to 50,000 units daily or even higher is justifiable when a moderately severe deficiency exists. It is probable that smaller doses are effective, although there is no contraindication to the larger doses since storage of the excess is quite efficient. It is of interest that some investigators have found it necessary to use as much as 1,000,000 I.U. to effect demonstra-

ble improvement in dark adaptation, while others
have obtained measurable changes with as little as
5,000-10,000 I.U. With large doses, the improvement
has been noted within two hours, and rises in the
blood level paralleled this rate of change. For most
average cases, a dose of 10,000 to 25,000 I.U. daily
is adequate for moderate and borderline deficiencies.
The Council on Foods of the American Medical Asso-
ciation recommends 25,000 I. U. twice daily for two
months or longer in acute deficiency states, and 25,000
I. U. two or three times daily for an indefinite period
for chronic deficiencies. Unfortunately, many people
continue to complain of defective vision when the sun
goes down, even after prolonged treatment with mas-
sive doses of vitamin A. The nature of the pathologic
process in these cases has not been clarified, but it may
involve either defective absorption or poor tissue utili-
zation. The latter type has been improved in a limited
number of cases by the addition of 3-5 mg. of riboflavin
or 100-200 mg. of ascorbic acid daily to the vitamin A
supplements

The most convenient form in which vitamin A can
be administered is fish liver oil concentrates. These
may be obtained in many different forms containing
vitamin A in concentrations up to 60,000 I.U. per cc.
Such preparations are usually efficiently absorbed
from the gastro-intestinal tract and may be given
orally unless some specific pathologic process which
contraindicates this route is known to be present.
Highly concentrated preparations of carotene are
likewise available for oral use and administration.

Parenteral administration by subcutaneous or preferably intramuscular injection is rarely necessary and, as a regular routine, should probably be avoided since injections of oil are likely to be painful and may lead to localized areas of fibrosis.

Vitamin A and carotene are readily absorbed through the skin. Accurate dosage by this route is obviously difficult, but it provides an alternative to other methods.

Because xerophthalmia and keratomalacia occur so rarely in the United States, they do not present a particularly important therapeutic problem here. This is more or less true of many other countries with the possible exception of the Orient! Under abnormal conditions of food shortage, however, as during World Wars I and II, these diseases have appeared in unprecedented epidemic form. Indeed their true incidence during the recent struggle will not be known for many years. They represent the most severe form of vitamin A deficiency, and they involve the hazard of permanent disability from blindness. Treatment obviously consists in supplying the missing dietary factor in large quantities, usually not exceeding 50,000 to 100,000 I.U. daily. The prognosis is excellent provided the disease has not progressed to the stage of corneal ulceration.

The existence of some factor in the nonsaponifiable fraction of cod liver oil which has a healing action on epithelial ulcerations of various sorts, particularly on those caused by tuberculosis, has recently been studied. This effect is possibly due to a bactericidal

power as well as to the epithelium-stimulating action of these preparations, the active constituent of which is almost certainly vitamin A or one of its esters. This general principle has been put to practical use through the incorporation of vitamin A into salves and ointments which are used in the treatment of ulcerations and infections of the skin. Results have not been uniformly good, although some of the animal experiments have been clearcut and well controlled. Such ointments usually contain 5-25 per cent of halibut or cod liver oil. It appears unwise to attempt final evaluation of this matter at present.

The occurrence of renal calculi as a complication in vitamin A deficiency, and as bearing a definite etiologic relationship to nutritional status, has not been well substantiated by more recent investigations despite animal experiments which pointed to that conclusion. Consequently, there seems to be no valid reason to administer vitamin therapy.

The recent interest in the use of vitamin A concentrates in large dosage for the treatment of hypertension deserves mention. Reported originally by two Cuban investigators, the effect has been confirmed in dogs rendered hypertensive by the Goldblatt technic. Dosages used in both human and animal studies have been as high as 400,000 I. U. daily by mouth. Although the effect can be reproduced with uniformity, it is now known to be unrelated to vitamin A and to depend rather on some other unidentified fraction of various marine and vegetable oils. Grollman[4] believes that the

[4] Grollman, A.: J. Pharmacol. & Exper. Therap., 84:128, 1945.

active principle may be derived from the oxidation of an unsaturated fatty acid or some other esterifiable substance, and there is reason to believe that it may be related to the depressor principle in some renal extracts. The entire subject is under further investigation, but thus far clinical trials have not been promising.

Vitamin A, like most of the other vitamins, has been used with unbounded enthusiasm in the treatment of almost every conceivable pathologic condition. In a large proportion of the reports in the literature no deficiency was proved or even thought to exist before therapy was begun. Fortunately, the toxicity of vitamin A is negligible so that it may be administered with no specific reservations. Up to the present, however, uses for this vitamin which have stood the test of time have unquestionably been in cases in which a lack of this substance was known to exist, through inadequacy of the diet, failure of absorption or faulty utilization in the tissues.

TABLE 2.—Recommended Dietary Allowances
(Food and Nutrition Board, National Research Council)

	Calories	Protein, Gm.	Calcium, Gm.	Iron, Mg.	Vit. A, I.U.	Thiamine, Mg.	Ribo-flavin, Mg.	Niacin, Mg.	Ascorbic Acid, Mg.	Vit. D, I.U.
Man (70 Kg.)										
Moderately active..	3,000	70	0.8	12	5,000	1.5	2.0	15	75	5
Very active........	4,500	70	0.8	12	5,000	2.0	2.6	20	75	5
Sedentary.........	2,500	70	0.8	12	5,000	1.2	1.6	12	75	5
Woman (56 Kg.)										
Moderately active..	2,500	60	0.8	12	5,000	1.2	1.6	12	70	5
Very active........	3,000	60	0.8	12	5,000	1.5	2.0	15	70	5
Sedentary.........	2,100	60	0.8	12	5,000	1.1	1.5	11	70	5
Pregnancy (latter half).....	2,500	85	1.5	15	6,000	1.8	2.5	18	100	400–800
Lactation.........	3,000	100	2.0	15	8,000	2.0	3.0	20	150	400–800
Children up to 12										
Under 1 year	100/Kg.	3.5/Kg.	1.0	6	1,500	0.4	0.6	4	30	400–800
1–3 years..........	1,200	40	1.0	7	2,000	0.6	0.9	6	35	400
4–6 years..........	1,600	50	1.0	8	2,500	0.8	1.2	8	50	400
7–9 years..........	2,000	60	1.0	10	3,500	1.0	1.5	10	60	400
10–12 years........	2,500	70	1.2	12	4,500	1.2	1.8	12	75	400
Children over 12										
Girls, 13–15 years..	2,600	80	1.3	15	5,000	1.3	2.0	13	80	400
16–20 years..	2,400	75	1.0	15	5,000	1.2	1.8	12	80	400
Boys, 13–15 years..	3,200	85	1.4	15	5,000	1.5	2.0	15	90	400
16–20 years..	3,800	100	1.4	15	6,000	1.8	2.5	18	100	400

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Chapter III

THE VITAMIN B COMPLEX

The vitamin B complex comprises a group of water-soluble factors, more or less closely associated in their natural occurrence, many of which have not yet been shown to be of significance in human nutrition. Knowledge of this entire group of substances has come slowly as an outgrowth of investigations of the etiology of beriberi.

The concept of beriberi as a deficiency disease was first suggested about 1906 by Grijns and Eijkman, Dutch medical officers working in the Netherlands Indies, where that condition is endemic. Isolation of the missing factor was accomplished by Funk in 1911, who also suggested that the term "vitamine" be applied to all such accessory substances in nutrition. In 1916 McCollum proposed the name water-soluble B for the antiberiberi factor. Later, in 1920, Drummond revised this nomenclature so that the accessory food substances known at that time were afterward designated vitamins A, B, C, D, etc.

Realization that vitamin B really consisted of a group of important dietary factors dates back to about 1920. This concept was materially strengthened when Goldberger and Tanner in 1925 announced that pellagra was also a deficiency disease which was preventable or curable by means of brewers' yeast. These

workers therefore recognized at least two constituents, vitamin B and the P-P factor (pellagra-preventive).

It was not until 1933 that Kuhn and his co-workers isolated from egg white and milk whey a yellowish-green fluorescent pigment which had important nutritional value for rats. They named this substance vitamin B_2. It has since been identified as riboflavin

VITAMIN B COMPLEX

THIAMINE B_1

B_2 COMPLEX

RIBOFLAVIN

FOLIC ACID

NIACIN

BIOTIN

PYRIDOXINE

PARA AMINO BENZOIC ACID

PANTOTHENIC ACID

INOSITOL

CHOLINE
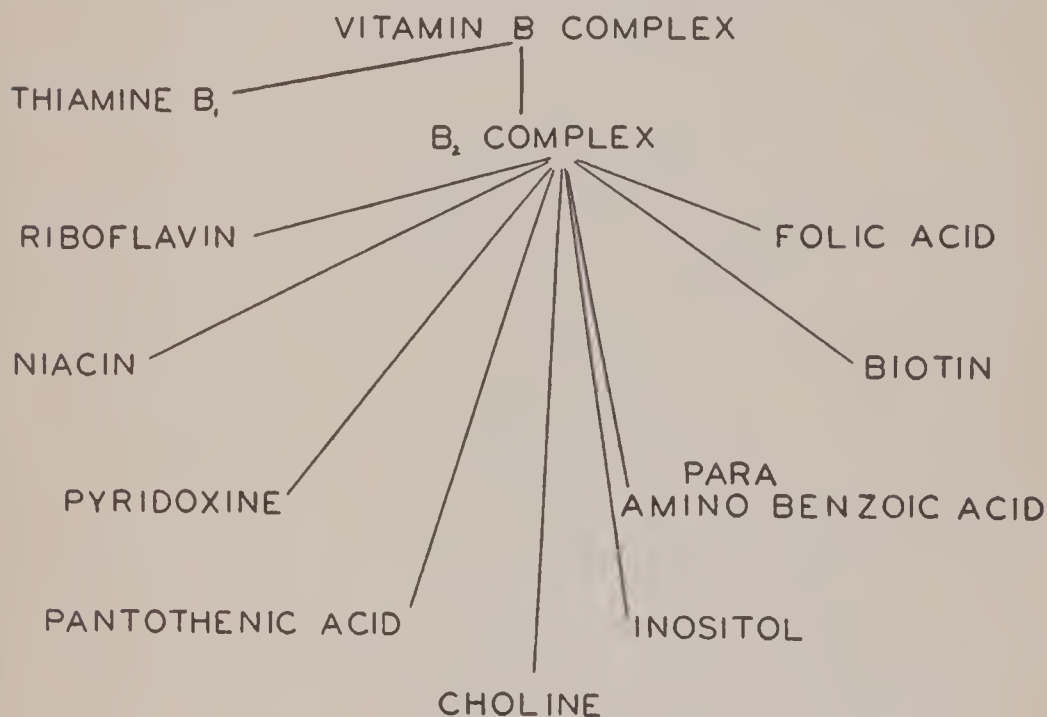
Fig. 7.—Scheme of vitamin B complex.

and is known to be identical with the "cytoflav" obtained by Banga and Szent-Györgyi in 1932 from heart muscle. The compound is of the utmost importance in biologic oxidations and intracellular respiration. In 1929, the American Society of Biological Chemists designated this factor vitamin G; unfortunately this term has been widely and erroneously used to refer to the entire B complex, exclusive of B_1.

The history of the development of our knowledge

of the B complex is long and complicated. Its resolution into 10 known chemical compounds and at least one other factor not yet chemically identified has involved vast painstaking research in scores of laboratories. The present conception of the structure of the vitamin B complex is illustrated in Figure 7.

As these components have been identified in pure form, some overlapping of biologic effects has been recognized, with resulting simplification of many details relating to the nutritional requirements of various species of experimental animals. In addition, certain effects formerly ascribed to vitamin fractions now appear to be attributable to amino-acids. Throughout the laborious task of unraveling the complex vitamin B group, one additional circumstance has gradually assumed increasing importance in animal nutrition. This is the bacterial synthesis of various nutrients in the intestinal tract of animals and subsequent absorption in amounts sufficient to affect the dietary requirements significantly. Thus, if an animal's diet supplies the nutritional factors necessary for growth of certain specific intestinal micro-organisms, other nutrients needed by the animal may be synthesized by this bacterial growth and so be made available to the host through intestinal absorption. An example of this mechanism is biotin, produced in adequate amounts by the intestinal flora of most species provided the growth requirements of these organisms can be supplied from external sources through the diet. This is probably the reason why biotin deficiency in most animals, and in man, is not seen under natural conditions and can be

produced experimentally either by the oral administration of avidin in amounts sufficient to combine with the biotin of bacterial origin or by quantitative reduction of the intestinal flora by drugs such as sulfasuxidine and sulfaguanidine.

From experimental data it is clear that this "endogenous" source of vitamins plays an important part in the nutrition of most animal species, including man. This aspect of the problem is receiving increasing attention in experimental animal work, but it has barely been explored in clinical studies. Indeed, it is difficult to predict what practical significance this mechanism may ultimately have in the science of human nutrition.

The following factors are now available in pure form, their respective chemical structures are known and they are being prepared synthetically on a commercial scale: (1) antineuritic, antiberiberi vitamin B_1, or thiamine; (2) riboflavin; (3) nicotinic acid, the P-P factor, or niacin; (4) rat antidermatitis factor, vitamin B_6, or pyridoxine; (5) chick antidermatitis factor, or pantothenic acid; (6) choline; (7) inositol; (8) para-aminobenzoic acid, probably an anti-gray hair factor in some animal species; (9) biotin, or the "egg white injury factor"; (10) folic acid, vitamin M, vitamin B_c, or the Lactobacillus casei factor.

THIAMINE

Although attempts to isolate the pure antineuritic vitamin were made before 1920 and continued throughout the next decade and a half, actual isolation in large enough amounts for study was not accomplished until 1934. Identification and synthesis by Williams and his co-workers followed in 1936 and 1937. The name thiamine, proposed by Williams because of its chemical structure, was accepted by the American Conference on Vitamin Standardization and the Council of Pharmacy and Chemistry of the American Medical Association in preference to the older name aneurin, proposed by Jansen of the Netherlands, who first isolated the substance from natural sources in 1926. The vitamin is still known as aneurin in Europe, but in the United States it is now officially called thiamine. It is generally felt that wide acceptance of a proper identifying name for each vitamin is distinctly to be hoped for, since it will tend to eliminate much of the confusion arising from the use of alphabetic designation. This change in nomenclature, of course, cannot proceed faster than the identification and synthesis of the various component fractions.

The structure of thiamine is shown in Figure 8. It consists of two distinct portions, a thiazole and a

pyrimidine moiety. These can be readily split apart with loss of biologic potency, particularly in neutral or alkaline mediums. The chemical properties of the compound have great importance in its stability under
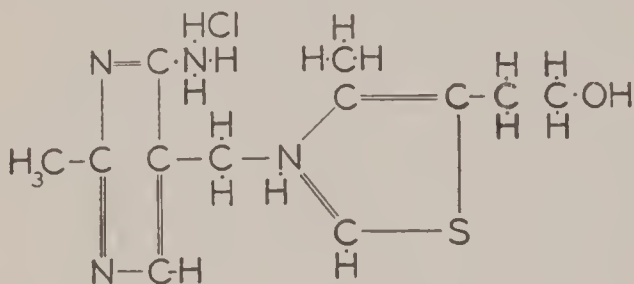
Fig. 8.—Vitamin B₁ (thiamine hydrochloride).

normal conditions. It is probable that thiamine functions in the body chiefly if not entirely in the form of the phosphoric ester, called cocarboxylase, which has the structure shown in Figure 9. As its name
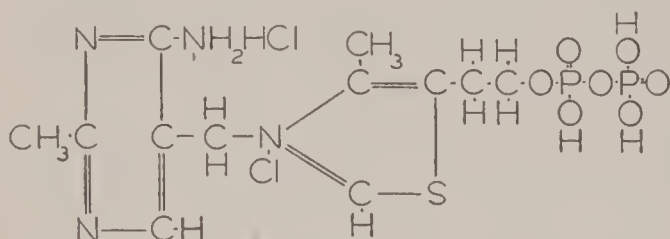
Fig. 9.—Thiamine pyrophosphate (cocarboxylase).

implies, this compound acts in the capacity of a co-enzyme to facilitate the decarboxylation or splitting off of carbon dioxide under certain circumstances, and in animal physiology it is concerned with the metabolism of pyruvic acid according to the equation shown in Figure 10. By means of a simultaneous oxidation, acetic acid rather than acetaldehyde becomes the end-product of the reaction. The enzyme, carboxylase, which catalyzes this reaction has re-

cently been found to be a compound of magnesium, diphosphothiamine and a protein, with a molecular weight around 75,000. This enzyme may also be important in the metabolism of keto acids other than pyruvic, and it may be involved in the interconversion of various sugars in vivo, in the synthesis of glucose from lactic acid, in the synthesis of fat from carbohydrate and in the synthesis of acetylcholine.

In the absence of adequate reserves of thiamine, pyruvic acid accumulates in both blood and tissues. This has been found to be true not only in experimental animals on deficiency rations but also in human cases of beriberi. About this well recognized chemical fact have centered efforts to develop a chem-

$$CH_3CO\text{-}COOH \xrightarrow{\text{(COCARBOXYLASE)}} CH_3CHO + CO_2$$

PYRUVIC ACID   ACETALDEHYDE
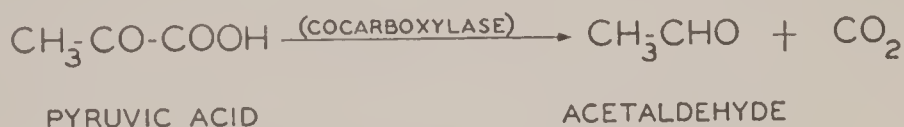
Fig. 10.—Equation for pyruvic acid.

ical test for diagnosis of thiamine deficiency, applicable to mild clinical cases. Unfortunately, the results have thus far been disappointing, owing to the difficulty of finding simple, workable methods for determining pyruvic acid specifically in the presence of other interfering substances such as acetone. Another obstacle to the use of such a method is the general failure to find elevated blood pyruvate levels in early and mild thiamine deficiency, under which conditions the test would be of the greatest value. Tissue stores of the vitamin, almost entirely in the form of diphosphothiamine, become depleted in the deficiency state, and the lowering of the content of

that substance in the brain has been shown experimentally to parallel the appearance of nervous symptoms.

Although the defect in pyruvate metabolism is the only specific biochemical lesion that has been positively identified in thiamine deficiency, it has been shown that a thiamine-like substance is released from a frog heart stimulated through the vagus nerve. The exact source of this factor is unknown, but it may be from either muscle or nerve. The experiments are suggestive only and are not at present applicable to human physiology.

Thiamine occurs in greatest abundance in yeast, in the germ layers and outer portions of cereal grains and in the organs and tissues of animals. Although many foods contain appreciable amounts of the B complex, concentrations in any single food are usually so small that the daily needs of any individual must be satisfied from several sources. Since the cereal grains have come to be so highly refined, there has been a significant and serious reduction in their thiamine content. Cowgill pointed out some time ago the disturbing, even alarming, trend of the American dietary toward a higher and higher carbohydrate intake with a simultaneous steady reduction in thiamine content. To quote some of his figures: the old type of wheat flour prepared during the early days of modern milling contained about 1.65 I. U. per Gm., a content which respresented about 62 per cent of the total vitamin originally present in the wheat. In contrast, modern milling methods have largely eliminated the thiamine-bearing portions of the grain,

so that at present the content averages only 0.15 I. U. per Gm., or 5.5 per cent of the original thiamine content of the wheat. Since sugar, which carries no thiamine, together with wheat flour provides about 42 per cent of total calories in the present American dietary, the serious implication of overmilling of grains becomes apparent. It seems probable that, in particular, the poorer classes in this country are subsisting on diets which are inadequate so far as thiamine content is concerned.

Because of this situation various agencies, including the Federal government, have become aware of the importance of fortification of wheat flour with the object of restoring its nutritional qualities. Table 3, representing the joint recommendations of the

TABLE 3.—AVERAGE VALUES FOR WHOLE WHEAT, WHITE AND
ENRICHED FLOUR*

PRODUCT	CAL-CIUM	PHOS-PHORUS	IRON	THIA-MINE	RIBO-FLAVIN	NIACIN	VITAMIN D
Whole wheat flour....	240	1,700	18.0	2.04	1.13	12.3†	. . . .
White flour.........	72	460	4.5	0.23	0.18	3.7	. . . .
Enriched flour							
Minimum enriched.	500	. . . .	6.0	1.66	1.2	6.0	250
Maximum enriched.	2,000	. . . .	24.0	2.50	1.8	9.0†	1,000

* Figures are in milligrams per pound except for vitamin D which is in U. S. P. units per pound.

† More recent assays have shown a niacin content of whole wheat flour of 20–24 mg. per pound. The maximum enrichment limit has been approved at 24 mg.

Council on Foods and Nutrition of the American Medical Association and the Nutrition Committee of the National Research Council, has been widely accepted as a reasonable standard for the "enrichment" program. Driven forward by the difficult and

pressing problems of nutrition in wartime, the fortification of flour gained widespread support and is now helping significantly to ameliorate the general nutritional status. In 1944 it was estimated that 75 per cent of American families were using enriched flour, and the benefits are clearly detectable.

Flour and bread were selected for enrichment because of their widespread daily use and because they are cheap enough to be used by even the lowest income groups, which are in greatest need of improved nutrition. However, despite the fact that enrichment adds an estimated cost of only 20 cents per capita per year, the price increment is depriving many families in the low income bracket of the benefits of the improved flour. A wider dissemination of knowledge will gradually correct this difficulty.

Wider use of whole wheat flour would also improve nutrition, but it is well known that dietary habits are extremely resistant to change. Statistics show a preference of 97:3 for white over whole wheat bread among the American people, so the reason for concentration of attention on the nutritional qualities of white bread is self-evident. Table 4 shows the present stand-

TABLE 4.—ENRICHMENT STANDARDS*
(Milligrams per pound unless otherwise stated)

Required	Flour Standard		Bread Standard	
	Min.	Max.	Min.	Max.
Thiamine	2.0	2.5	1.1	1.8
Riboflavin	1.2	1.5	0.7	1.6
Niacin	16.0	20.0	10.0	15.0
Iron	13.0	16.5	8.0	12.5
Optional				
Calcium	500	1,500	300	800
Vitamin D (U.S.P. units)	250	1,000	150	750

* Figures from the National Research Council Bulletin no. 110 (1945).

ards accepted for the enrichment of flour and bread.

The position of the National Research Council on enrichment of bread has been challenged by numerous writers on the basis of poor and inadequate knowledge of the existence of suboptimal nutrition in the popula-

TABLE 5.—THIAMINE CONTENT OF FOODS*

	MG. PER 100 GM.		MG. PER 100 GM.
Beef	0.12	Whole white bread,	
Veal	0.18	enriched	0.24
Liver, fresh	0.27	Asparagus	0.16
Heart, fresh	0.54	Carrots	0.07
Chicken	0.11	Cauliflower	0.10
Lamb	0.20	Onions	0.03
Pork	0.89	Lettuce	0.06
Bacon	0.42	Potatoes	0.11
Milk, whole	0.04	Spinach	0.12
Milk, skim	0.04	Squash	0.05
Cheese	0.04	Cabbage	0.07
Egg	0.12	Beans, lima, green	0.25
Egg yolk	0.32	Beans, string	0.08
Barley cereal	0.12	Peas, canned	0.11
Oatmeal	0.55	Peas, dried split	0.87
Rice, polished	0.05	Peas, green	0.36
Rice, brown	0.29	Almonds	0.25
Rye flour	0.47	Pecans	0.72
Whole wheat flour	0.56	Walnuts	0.48
Wheat flour, enriched	0.44	Peanuts	0.30
Whole wheat bread	0.28	Apples	0.04

* These figures are from Tables of Food Composition prepared by the Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, in cooperation with the National Research Council, Miscellaneous Publication no. 572 (1945). Nutritive values are given for foods as brought into the house for consumption; no account has been taken of losses of food value that may occur in preparation of meals.

tion in general. McHenry[1] considered the recommended allowances too high and Lepkovsky[2] has advocated the widespread use of whole wheat bread. It is clear that much more information is needed before this problem can be settled.

Other significant sources of thiamine are shown in Table 5. It is immediately apparent that vegetables are

[1] McHenry, E. W.: Canad. M. A. J., 52:147, 1945.
[2] Lepkovsky, S.: Physiol. Rev., 24:239, 1944.

not as good a source of thiamine as most laymen be-
lieve. If cereal grains, because of excessive processing,
are removed from their position of pre-eminence as
sources of thiamine, meats, particularly pork, beef and
liver, leguminous vegetables, nuts and eggs may be con-
sidered the best and most available sources of thiamine
in the average American dietary. The thiamine of
yeast is best absorbed after drying or cooking, for live
yeast cells do not readily give up their thiamine but tend
to pass intact through the intestinal tract without rup-
ture of the cell membrane.

Thiamine is quite resistant to heat, particularly in
the absence of alkali, and for this reason destruction by
cooking is usually minimal. Except for leaching in boil-
ing water and the subsequent discarding of the water,
which removes large amounts of thiamine from vege-
tables, the usual methods of preparing food remove
25-40 per cent of the thiamine present. This probably
occurs chiefly through the splitting of the molecule into
its two constituent parts and conjugation of other sub-
stances with the vitamin, rather than through oxida-
tion. Thiamine destruction in the cooking of vegetables,
when the cooking water is discarded, may amount to
20-35 per cent. This loss is increased when bicarbonate
is added, particularly with some types of vegetables.

The roasting of pork loin causes a 43-50 per cent
loss, or about three times that occurring when the
meat is braised. Double boiler cooking of cereals
spares nearly all the thiamine. Baking of bread
causes about a 15 per cent destruction of the thiamine
in the original constituents. Both quick freezing and

pressure cooking are sparing of thiamine. The latter process should be carried out as quickly as possible with a minimum of water added, since destruction of the vitamin is largely a function of time. In this connection it should be noted that losses up to 90 per cent in thiamine have been noted in cafeteria and restaurant foods kept for prolonged periods on a steam table.

The daily requirement of thiamine for normal healthy adults as originally determined in the investigations of Cowgill was established at about 330 I. U. or 1 mg. This figure has been revised upward and downward by various investigators, and the matter still cannot be considered settled. Some older estimates set 0.6 mg. as an optimal intake, but Keys and his associates[3] reported that an intake in excess of 0.23 mg. per 1,000 calories of food did not provide any additional benefit. Another study[4] demonstrated the apparent adequacy of 0.47 mg. daily. The older estimates are still considered by many authorities to approach more closely to true optimal needs. Taking body size, food consumption and activity into consideration, therefore, adults may require from 0.5 to 2.5 mg. daily for the best nutrition. The National Research Council recommends 1.5 mg. daily for a moderately active adult male. In recognition of the thiamine to calorie ratio, Cowgill long ago suggested the formula: thiamine requirement = body weight × caloric requirement × a constant. Thus, a small man eating a heavy

3 Keys, A.; Henschel, A. F.; Mickelsen, O., and Brozek, J. M.: J. Nutrition, 26:399, 1943.
4 Holt, L. E.: Pennsylvania M. J., 46:451, 1943.

diet because of strenuous physical work may require more thiamine than a large man leading a sedentary existence.

Another factor of the greatest importance in determining the thiamine requirement is the proportion of fat to carbohydrate in the diet. It is now well established that fat has a thiamine-sparing action, while carbohydrate increases the need. This is well illustrated in animal experiments which reveal a greatly increased latent period before deficiency symptoms begin to appear when the deficient diet contains a high proportion of fat, as compared to the latent period under similar circumstances when carbohydrate supplies the greater part of the caloric intake. This relationship has been so thoroughly studied that some investigators believe that the thiamine requirement for an individual is proportional only to the total nonfat calories in the diet. Whatever the mathematical relationship eventually may turn out to be, an additional explanation is provided, through this concept, for the appearance of beriberi in a population which subsists chiefly on polished rice, very low in thiamine and unusually high in carbohydrate. It also explains the familiar clinical observation that deficiency manifestations following prolonged periods of inadequate food intake often begin to appear, or become much accentuated, as soon as the patient receives large amounts of glucose and saline in treatment for dehydration and starvation.

The rôle of intestinal biosynthesis of thiamine in the altering of the human requirement is unknown, but the

evidence suggests that it may be a significant factor. Absorption from the colon is rather poor, but under conditions of stress enough thiamine may well be made available to the animal through this route to delay significantly the appearance of deficiency manifestations.

Another factor to consider when evaluating human requirements is environmental temperature. Studies by Mills had suggested a greatly increased need for thiamine by experimental animals subjected to high temperatures. More recent work,[5] however, has produced even better evidence that tropical requirements are less rather than more than normal, possibly related to the lower intake of food in hot climates.

Diseases Caused by Thiamine Deficiency

Beriberi.—This disease, as it exists in the Orient, is practically nonexistent in this country. Nevertheless various modifications of the disease in severe form are seen in the United States, and the same underlying pathologic physiology in all types causes a definite similarity in the clinical manifestations.

In adults the disease is nearly always chronic, beginning with weakness, anorexia, fatigue and many vague aches and pains in various parts of the body. Nervousness, headache, tenderness of muscles and rapid heart rate are also noted rather early. Involvement of the nervous system produces both signs and symptoms of ascending peripheral neuritis, charac-

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[5] Kline, O. L.; Friedman, L., and Nelson, E. M.: J. Nutrition, 29:35, 1945.

terized by severe pains in the muscles, with weakness
and cramping in the legs. There is also a burning
type of pain usually around the feet. Paresthesias de-
velop in sharply outlined areas, and the deep tendon
reflexes, particularly in the legs, become diminished
and then disappear completely. Footdrop appears,
associated with extreme weakness of all the muscles,
and marked sensitivity to deep pressure over the
nerve trunks. Involvement of the upper extremities
usually appears later. As the nerve involvement be-
comes greater, muscle atrophy and trophic skin
changes appear. All peripheral nerves in the body are
susceptible, not excluding sympathetic and parasym-
pathetic systems. The vagi are particularly affected.

It should be noted in this connection that there is
now accumulating excellent evidence that the his-
tologic degenerative changes in peripheral nerves in
beriberi are not due to thiamine deficiency only but
to a lack of other factors as well, the exact identity
of which is not known. The improvement which oc-
curs following thiamine administration is apparently
due in part to the effect on appetite, which results in
an increase in the amount and type of food ingested.
This fact, known for some time in relation to experi-
mental deficiencies, has only recently been shown to
apply also to human disease.

Meanwhile, edema usually begins to appear, first
about the feet and ankles but gradually ascending
until eventually ascites, hydrothorax and complete
anasarca develop. This manifestation is chiefly a con-
sequence of hypoproteinemia, but later in the disease

is aggravated by cardiac edema secondary to beri-
beri heart. Inasmuch as severe and even fatal beriberi
without edema has been observed with a total plasma
protein level of 1.8 Gm., there are obviously factors
other than hypoproteinemia involved in the pathogen-
esis of the edema. With other types of anasarca, this
fluid accumulation is now thought to be associated with
an injury to the capillary wall resulting in a change in
permeability which permits passage of an excess of
fluid into the tissues.

Cardiovascular symptoms are those common to
heart disease of any etiology but in this instance may
be remarkable for their suddenness of appearance.
Tachycardia, present early in the disease, may lead
without warning to cardiac failure as evidenced by
dyspnea, cyanosis, weak, thready pulse and occasion-
ally pain of anginal type. Murmurs are usually audi-
ble, the precordial impulse is forceful and heaving
and the heart markedly enlarged. Venous pressure is
elevated: the liver is enlarged, painful and pulsating.

Electrocardiographic changes consist chiefly in a
flattening or disappearance of the T waves and a
lengthening of the S-T segment. Extrasystoles are
not unusual (Figs. 11A and 11B).

Examination of the blood usually shows secondary
anemia, the appearance of which is difficult to relate
specifically to thiamine deficiency. Serum protein
values are low, nearly always below the critical level
for edema formation. Blood sugar values tend to be
elevated, and cholesterol levels are depressed. Platt
and Lu have reported, in addition, increased amounts
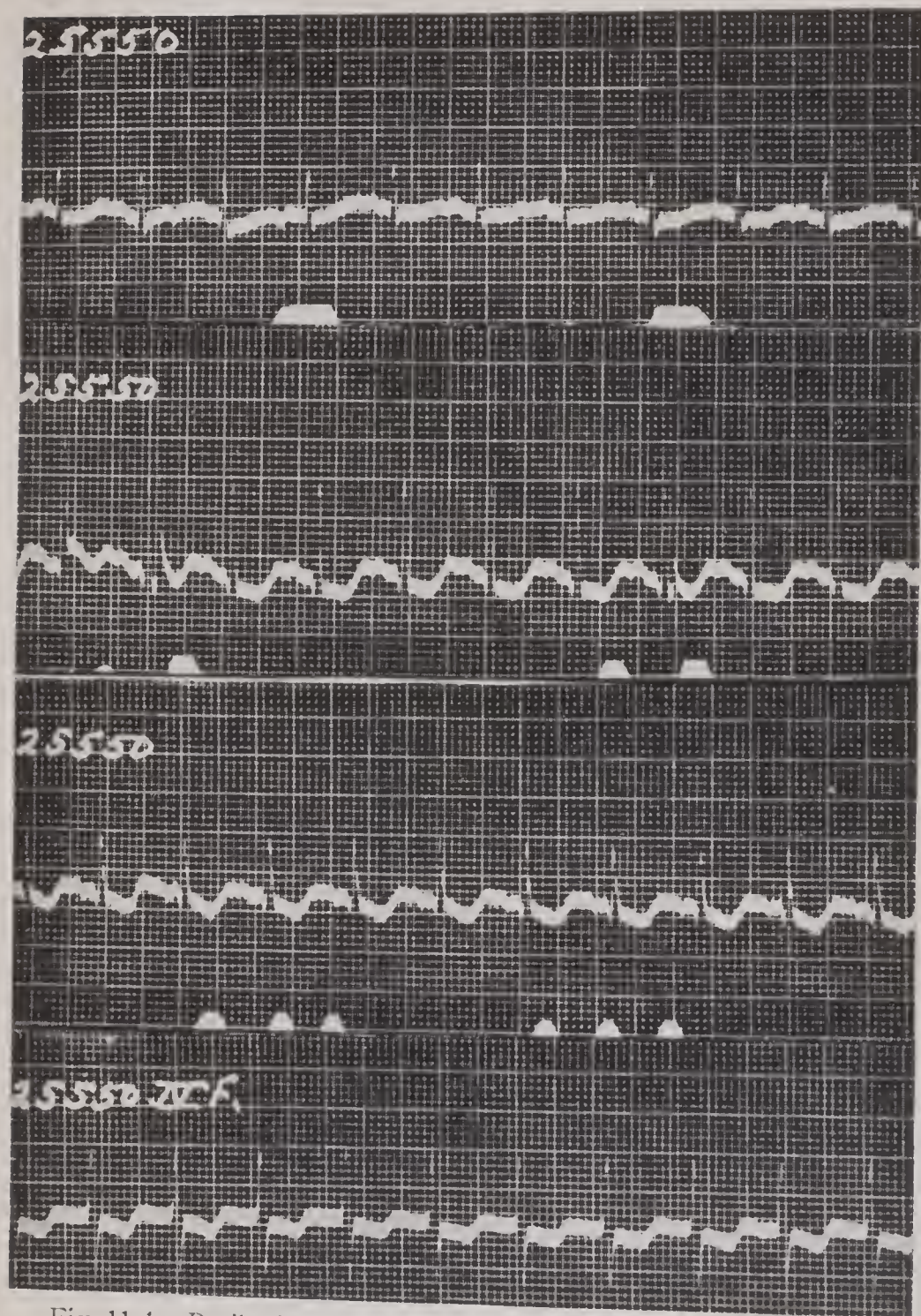
Fig. 11.*A*.—Beriberi, before therapy. Tachycardia is present (rate 135-140) with depression of S-T segment and lowering of T waves. No history of digitalis medication.
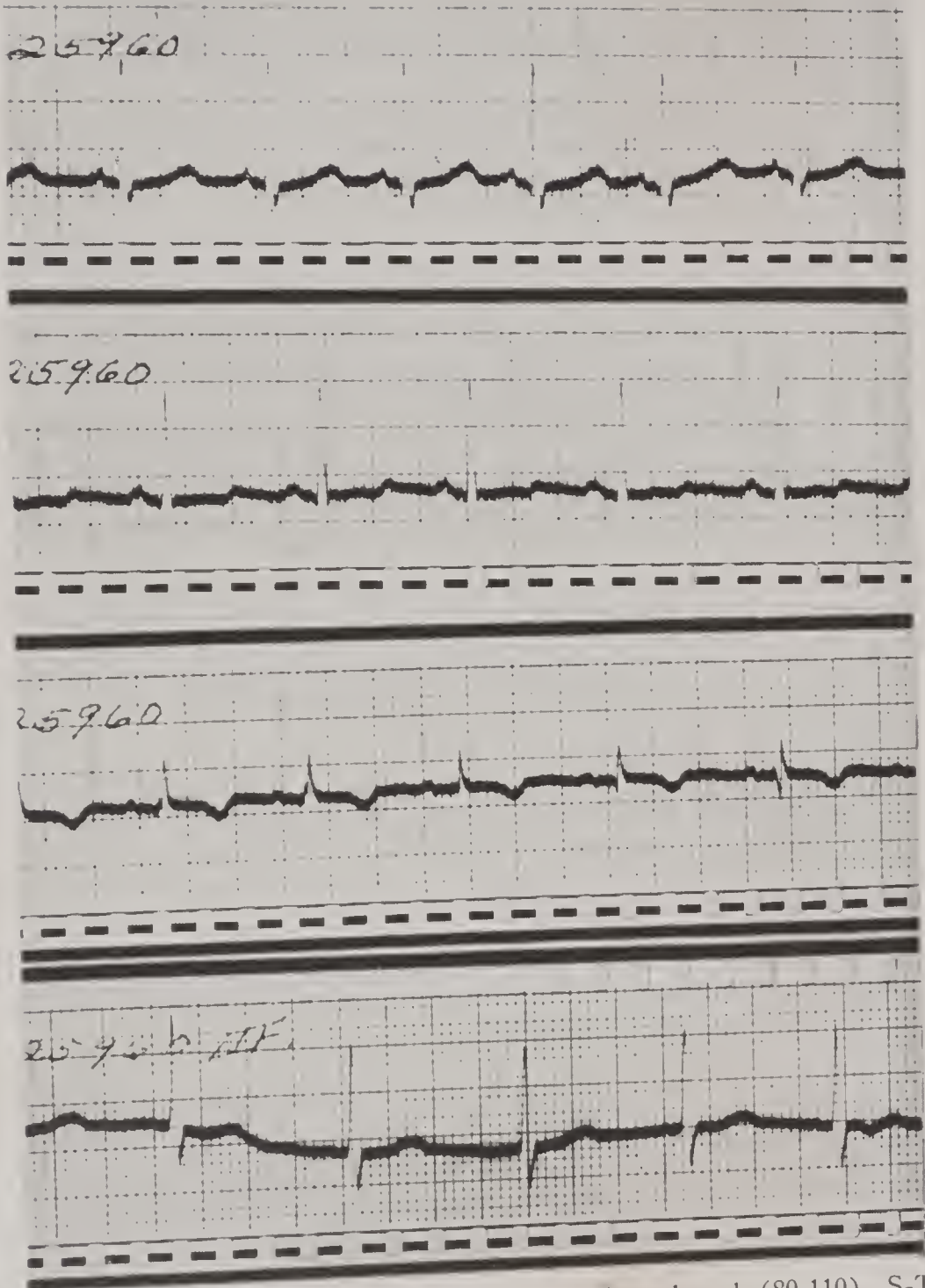
Fig. 11*B*.—Beriberi, after therapy. Rate has slowed (80-110), S-T segments are nearly iso-electric and T waves are increased in amplitude, particularly in leads I and IV.

of "bisulfite-binding substance," which is presumably pyruvic acid, in cases of beriberi.

The disease is known to occur in the wet form, in which the edema and anasarca are conspicuous, in the dry form, in which the neurologic manifestations predominate, and in a mixed form showing evidences of cardiac disease as well as the signs of the other types of beriberi. There is no reason to believe that the etiology differs in the various types; they probably represent merely individual variations. The wet form is rarely reported in the United States, possibly because the oriental type of the disease is so ill-defined at present and the pathogenesis in terms of dynamic physiology is almost completely obscure.

Infantile beriberi is a well recognized entity which is extremely common in some parts of the Orient but rather rare in this part of the world. It appears to be associated invariably with a poor maternal diet during pregnancy which produces a mild or "subclinical" type of maternal beriberi. Even a congenital case in a newborn infant has now been reported.

Beriberi Heart.—Although cardiovascular involvement in beriberi has been known almost as long as the disease, this aspect of heart disease has received special attention since Weiss and Wilkins in 1935 reported 35 cases of cardiac disorder which they demonstrated to be due to lack of thiamine and which they named beriberi heart. The clinical picture resembled that of true Oriental beriberi, particularly of the infantile type. Paroxysmal attacks of precordial pain, tachycardia, dyspnea, cyanosis, increased venous

pressure and the other usual signs of congestive failure are all present. The heart is regularly enlarged, often disproportionately to the right. Electrocardiographic changes are remarkably unimpressive and are those already described. Onset of the entire condition may be quite sudden, and signs of vasomotor collapse may also appear with alarming suddenness. In all cases reported by Weiss and Wilkins, the antecedent inadequate intake of food was apparent, and most of the patients were alcoholics. This disease is not common, probably because severe thiamine deficiency is unusual in the population as a whole. That cardiac disability on this basis may commonly be superimposed on heart disease of other common etiologies, however, must be recognized. When it does occur, the deficiency aspects of the situation may not be easily recognized. Many cardiologists regard the routine administration of thiamine in cardiac decompensation as a valuable part of therapy. In uncomplicated beriberi heart, therapy is specific and curative, and the response may be dramatic provided cardiac failure has not progressed too far. This condition is one of the few in which the size of the cardiac silhouette may decrease rapidly and markedly in response to treatment.

Blankenhorn[6] reevaluated the clinical syndrome of beriberi heart disease and listed the following criteria for establishing that diagnosis: (1) enlarged heart with normal sino-auricular rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral

6 Blankenhorn, M. A.: Ann. Int. Med., 23:398, 1945.

neuritis or pellagra, (5) nonspecific changes in the electrocardiogram, (6) absence of other recognized cause of heart failure, (7) grossly deficient diet for at least three months and (8) clinical improvement with reduction of heart size after specific treatment, or autopsy findings consistent with beriberi according to the criteria of the American Heart Association (1939). Failure to respond to digitalis therapy, as described by Weiss and Wilkins, might be added. Furthermore, the element of poor nutrition may be superimposed on any of the other well recognized causes for heart failure, so the clinician must be constantly alert to the possibility of this complicating factor in any patient seeming to show an abnormal response to the usual forms of therapy.

Alcoholic Polyneuritis.—Peripheral neuritis frequently appears in chronic alcoholic patients who regularly consume large quantities of distilled alcoholic liquors. Previously thought to be a specific toxic effect of the alcohol, this condition is now known definitely to be due to a nutritional deficiency caused by the replacement by alcohol of foods which contain the essential factors for normal nutrition. This concept was first suggested by Shattuck in 1928 and has since been confirmed by other investigators. It is now known that the polyneuritis of chronic alcoholism can be cured by adequate intake of proper food or vitamin supplements even when the original intake of alcohol is maintained throughout the period of therapy. The effect of alcohol in bringing about this deficiency state is clarified when it is pointed out

that, owing to the energy value of whisky, 1 qt. will provide approximately 2,800 calories. For a normal-sized adult, this represents the total energy requirement for 24 hours and eliminates all necessity or desire for other food. Since whisky contains no food value other than its alcoholic content, it is apparent that long-continued use of it in amounts even approaching 1 qt. daily will soon permit complete exhaustion of body stores of important nutritional factors. Superimposed on this mechanism are the gastritis which so frequently develops, accentuating still more the anorexia which already exists, and the important augmentation of thiamine requirement incident to a high carbohydrate intake. Thus, multiple deficiency manifestations begin to appear, one of the first and most important of which is peripheral neuritis, caused by specific lack of the vitamin B complex and more especially thiamine.

There have long been speculation and uncertainty concerning the rôle of thiamine in the metabolism of alcohol. Early evidence seemed to indicate that both thiamine and carbohydrate were needed for the oxidation of alcohol, but new data show instead a thiamine-sparing function of alcohol suggesting that in alcoholic polyneuritis the thiamine intake must be even lower than was previously calculated.

Evidence continues to accumulate that the tissue changes in the nervous system in polyneuritis of deficiency, regardless of its specific precipitating factors, are attributable to multiple deficiencies of, at least, other B complex components and perhaps of other fac-

tors also. Inadequate intake of riboflavin and panto-
thenic acid is almost certainly involved, and their re-
placement constitutes an important part of the therapy
of this disease.

The symptoms and signs are those of any severe
peripheral neuritis, with ascending weakness and pain
in the feet and legs. This pain is frequently cramp-
like but often of a burning character and of such
severity that narcotics are required for relief. The
weakness progresses to well defined footdrop, and the
sensory changes include hypesthesia, hyperesthesia
and eventually complete anesthesia of areas supplied
by the cutaneous nerves. Ordinarily the hands and
arms are not involved until late in the disease, at a
time when the leg manifestations are far advanced.
Only rarely, in the most severe cases, do the trunk
muscles and sensory nerves become involved. The
picture is identical with that which occurs in classic
beriberi; indeed, there is no real reason why the con-
dition should not be known as beriberi, since alcohol
is simply a contributory factor.

Polyneuritis of Pregnancy.—In the same manner
that alcoholic polyneuritis was once thought to be
due to a toxin, so the neuritis of pregnancy, associ-
ated almost invariably with excessive vomiting, was
thought to be caused by a toxin which caused not only
the vomiting but also the neuritis. Only gradually has
it become clear that this disease is actually a deficiency
condition, identical in many ways with true beriberi.
Its appearance always follows many weeks of vomit-
ing and low food intake. During this period, the preg-

nant woman gradually exhausts her liver glycogen stores and begins to oxidize fat to such an extent that ketosis usually appears. Although the ketosis is an indication of a lack of available carbohydrate, it nevertheless acts in a certain sense as a protective mechanism, for the fat diet has a thiamine-sparing action and thereby delays the onset of thiamine deficiency symptoms. Not infrequently the administration of intravenous glucose and saline for the treatment of dehydration provides enough carbohydrate to bring out sharply the thiamine deficiency which had been held in abeyance by the high fat diet.

The actual signs of this type of polyneuritis are identical in every respect with those of beriberi and those resulting from chronic alcoholism, and, as in those conditions, other deficiencies are almost certain to coexist. Thus, in any pregnant woman with hyperemesis gravidarum, deficiency disease should immediately be a major consideration, whether the neuritis has appeared or not.

The metabolic changes in pregnancy known to increase the need for some nutrients, such as protein, calcium, vitamin A and ascorbic acid, have a questionable effect on the thiamine requirement. Careful quantitative examination indicates the complete adequacy of a good, well balanced diet without added supplements, contradicting the former view that the heightened metabolism and the needs of the fetus together increased the thiamine requirement. The National Research Council recommends 1.8 mg. of thiamine daily during the latter half of pregnancy.

Hyperthyroidism.—Because of the relationship known to exist between caloric intake or metabolic demand and thiamine requirement, increasing attention has been paid recently to the whole nutritional aspect of thyrotoxicosis. Animal experiments have shown that thiamine in adequate amounts protects against thyroid intoxication up to a certain point. In human subjects whose diets are deficient in thiamine the metabolic rate increases less than in normal subjects after ingestion of desiccated thyroid. Thyrotoxic patients have lower blood levels of both thiamine and cocarboxylase than normal subjects. These and related observations help to substantiate the belief that in man, as in animals, thyrotoxicosis is associated with an increased requirement for thiamine. Although some diversity of opinion continues concerning the clinical application of these observations, thiamine administration has nevertheless been accepted in many clinics as an important part of the preoperative preparation of thyrotoxic patients. Evaluation of the resulting clinical reports is difficult, but the impression is widely established that the general nutritional status of the patient is improved partially, at least, because of a better appetite. Because of the data from animal experiments, liver glycogen stores are thought to be increased, and the patients seem to withstand surgery more easily than was the case before this therapy was used. Final evaluation of this matter is yet to be made, but the physiologic principles underlying the administration of thiamine supplements in conditions with increased basal metabolic rate are sound.

Diarrhea.—The mechanism thought to explain the appearance of deficiency disease in chronic ulcerative colitis is the greatly increased intestinal rate. Since many types of foods are inadequately digested in this disease simply because they pass through the entire intestinal tract too rapidly, it is reasonable to believe that many essential accessory food components will also be poorly absorbed. Thiamine is one of the most important of these; it is not stored in large amounts, and the threshold for the appearance of manifestations is relatively quite low. For these reasons it is not uncommon to find evidence of thiamine or B complex deficiency in ulcerative colitis or in any other condition in which there is severe, long-continued diarrhea. Indeed, a large part of the debility caused by such diseases is due to deficiencies of various sorts. Under these circumstances it is frequently desirable to administer the vitamin supplements parenterally whenever possible in order to insure their absorption. The water-soluble factors are otherwise effectively utilized by mouth, so that the oral route of administration is usually satisfactory.

The appearance of deficiency disease is equally logical in sprue, in which, in addition to diarrhea and a rapid intestinal rate there is reason to believe that intestinal absorption is seriously impaired. The developing deficiency state is accentuated by the further interference with intestinal absorption by that deficiency per se, so that a vicious circle may be estab-

lished which calls for parenteral vitamin therapy.

Anorexia.—Because anorexia is an early manifestation of experimental thiamine deficiency in animals, this substance has been extensively and indiscriminately used clinically as a stimulant to appetite. This therapeutic application is justified up to a certain point and often brings about gratifying results. It should be emphasized, however, that thiamine is effective only in the presence of a deficiency of that factor and to a degree in proportion to the severity of that deficiency. It is by no means successful in every case of poor appetite, and brilliant results should not be anticipated when there has been no preexisting lack of the vitamin in the diet, regardless of how poor that diet may have been in many other ways. Unfortunately there is no easy laboratory method for the diagnosis of mild states of thiamine undernutrition, so it is usually necessary to establish the presence of that condition by a therapeutic trial. Such a procedure is obviously harmless; the dosage need not be large or the trial period long, since the results will appear promptly if they are to appear at all.

The psychologic aspects of vitamin administration may be both interesting and important, but they may make true evaluation of the nutritional status very difficult. Indeed, there seems little doubt that much of the therapeutic success of indiscriminate vitamin administration is on a "psychic," not an "organic," basis.

Anorexia nervosa is a serious disease characterized by deep-seated psychic disturbances which lead the

patient to self-imposed starvation. Weight loss and cachexia may be extreme but, as in other forms of starvation, there is rarely any associated specific avitaminosis. Therapy is chiefly psychiatric, and no dramatic results should be expected from the administration of thiamine to stimulate appetite, since the disease is not primarily a deficiency state.

Pellagra.—Although this disease appears to be caused especially by a lack of the pellagra-preventive factor, nicotinic acid or niacin, it is nevertheless widely recognized as a multiple deficiency condition in which absence of thiamine from the diet plays an important part. Indeed it has been difficult to separate the portion of the clinical picture due to nicotinic acid deficiency from that part due to the need for other factors. The availability of various fractions of the B complex in pure crystalline form has made possible this separation. It now seems clear that the peripheral neuritis frequently seen in pellagra as well as the anorexia and peripheral edema are due to a concomitant lack of thiamine in the diet. Replacement of this vitamin in the diet will produce a marked improvement in the clinical condition of the patient, superimposed on the benefit derived from nicotinic acid therapy. The dosage of thiamine in this condition in no way differs from that in the other conditions of B_1 deficiency. This disease is more fully discussed in Chapter VI.

Wernicke's Syndrome.—Described originally by Wernicke in 1881, this clinical entity has gradually become associated with alcoholism despite the fact

that it may occur under other conditions of malnutrition. It is characterized by varying degrees of ophthalmoplegia, general ataxia, peripheral neuropathy and clouding of consciousness. Delirium either precedes or accompanies the appearance of the other manifestations, and a typical Korsakoff syndrome frequently follows in those patients who recover. The clinical picture is often confused by the coexistence of other deficiency lesions such as scurvy, pellagra and ariboflavinosis and is thought to be itself a deficiency disease, despite the fact that it has been difficult to associate its occurrence with a lack of any single specific dietary factor.

The pathologic lesions, while more or less diffuse, are usually concentrated in the region of the periventricular gray matter and consist of small foci of degeneration and scattered focal enlargements of the blood vessels. Additional contributions to the pathology of the disease were made by Riggs and Boles,[7] who have reported on 42 autopsies. From this study it appears that the disease is a pathologic entity which often shows such confused and ill-defined clinical manifestations that correlation with the lesions becomes difficult. Emphasis was again placed on the association of this condition with chronic alcoholism, fatty liver, peripheral neuropathy, extreme emaciation, edema, pellagrous dermatitis, stomatitis, cheilitis, etc., all of which lend support to the deficiency etiology. These authors concluded that acute infections and vomiting,

[7] Riggs, H. E., and Boles, R. S.: Quart. J. Stud. on Alcohol, 5:361, 1944.

superimposed on a deficiency state, might be precipitating factors. Whether Wernicke's disease will eventually be identified as a single, as yet unrecognized, or a multiple deficiency state is difficult to say.

The response to thiamine administration is highly satisfactory, particularly in relation to the ophthalmoplegia. The use of concentrates of the entire B complex as well as all other nutrients is necessary, however, since multiple deficiencies are invariably present.

It is of interest to note that the etiology of Chastek paralysis in foxes has been definitely identified as thiamine deficiency, and is considered the counterpart of Wernicke's syndrome in humans. This interesting disease in foxes is produced by a diet containing relatively large amounts of uncooked fish, and the mechanism of its pathogenesis appears to be a destruction of thiamine by an enzyme contained in the tissues of fresh water fish. Salt water varieties thus far tested do not seem to contain this material. Through the enzyme's action thiamine is split into its pyrimidine and thiazole portions with a loss of vitamin activity. If such an occurrence can be demonstrated in human subjects, the ingestion of raw fresh water fish by certain racial groups may be proved to have some etiologic significance in the development of beriberi.

Mild Thiamine Deficiency.—It is probably justifiable to discuss mild thiamine deficiency as a definite entity, because it has been repeatedly produced experimentally in human subjects, uncomplicated by other coexisting deficiencies. The clinical manifestations in all instances are approximately identical. The sub-

jects lose their appetites and many develop nausea
and vomiting. They become depressed, irritable, quar-
relsome, inefficient and forgetful. Many lose their
previous manual dexterity and become confused and
inattentive to details. A neurasthenia-like condition
is not uncommon, and responds promptly to the ad-
ministration of thiamine. It should not be inferred,
however, that all neurasthenics will be improved by
thiamine therapy since there are obviously many other
causes for the condition. Indeed considerable con-
fusion has been caused by the reported successful
treatment of this same condition with niacin, pyri-
doxine and vitamin E. Experimental production of
this condition in human subjects is attended by definite,
measurable biochemical changes in muscle, blood and
urine which parallel the subjective clinical manifesta-
tions. All of these changes can be detected as early as
two weeks after beginning a diet which provides only
0.2 mg. of thiamine daily. Detailed observations have
been reported by Hulse and his associates.[8]

Thiamine and Sexual Function.—A considerable
series of investigations has produced evidence of the
need for adequate supplies of several vitamins of the
B group for normal ovarian function. Under normal
physiologic conditions a significant amount of estrogen
is inactivated by the liver, probably by some enzymatic
process which requires at least thiamine and riboflavin.
In the absence of these vitamins the inactivation does
not take place, as measured by several different experi-

[8] Hulse, M. C.; Weissman, N.; Stotz, E.; Clinton, M., Jr., and Fer-
rebee, J. W.: Ann. Int. Med., 21 :440, 1944.

mental technics. Since a similar effect on androgen metabolism apparently does not take place, malnutrition may disturb the balance between these endocrine functions. Biskind[9] has applied this principle clinically in the management of various endocrine disorders, including menorrhagia, metrorrhagia, premenstrual tension, chronic cystic mastitis, gynecomastia, impotence and some types of sterility. The single factor thought to be common to all these conditions is a degree of malnutrition sufficient to impair liver function to the extent of rendering the liver incapable of maintaining a correct balance between androgens and estrogens. The administration of large supplements of thiamine, both orally and parenterally, has resulted in striking clinical improvement by correcting this metabolic defect. Not only does the clinical aspect of this work need further extensive exploration, but the therapeutic preparations may justifiably be extended to include riboflavin, on the basis of tissue studies which demonstrate its effect on estrogen metabolism. Furthermore, there is good reason to believe that inanition, at least in experimental animals, is as important as any specific vitamin deficiency in producing this result. Hertz and Sebrell[10] have also shown the importance of folic acid in the maintenance of normal ovarian function in experimental animals. In all experimental work of this kind it must be remembered that inanition rather than specific vitamin deficiencies may be partially responsible for the observed effects.

9 Biskind, M. S.: J. Clin. Endocrinol., 3:277, 1943.
10 Hertz, R., and Sebrell, W. H.: Science, 100:293, 1944.

Diabetes Mellitus.—The effects of vitamin deficiencies and vitamin supplements on the course of diabetes mellitus are poorly understood and deserve a great deal of attention. On the basis of an old observation that yeast is beneficial to diabetic patients, numerous attempts have been made to reduce insulin requirements. In experimental work with depancreatized dogs the serious effects of B complex deficiency and the remarkable improvement resulting from the restoration of these factors are unmistakable. On the clinical side, dramatic results have been reported from the use of B complex supplements by diabetic patients receiving apparently adequate diets. These results have been interpreted on the basis of two possible hypotheses: (1) the requirement for thiamine, and other B components, is higher in diabetic than in normal animals, and (2) the metabolic defect in diabetes consists, in part, in an impairment of liver function which prevents the action of normal amounts of insulin and thereby raises insulin requirements. Adequate vitamin supplements restore normal relationships by improving the capacity of the liver to respond. Although it is probably unreasonable to expect that nutrition therapy will revolutionize the treatment and prognosis in diabetes mellitus, it is quite possible that a more complete understanding of the mechanism of this phenomenon will lead to practical clinical help for diabetic patients.

Special consideration may properly be given to the rôle of thiamine in the treatment of diabetic neuritis. The frequent failure of this condition to respond to therapy with this vitamin is well known and may

probably be attributed to several factors. (1) With the poor peripheral circulation which frequently accompanies the neuropathy, there may be a continuing tissue deficiency of many nutrients even though they are present in the diet in adequate amounts. (2) Long-standing neuropathy associated with demonstrable, degenerative anatomic lesions usually does not respond even to excessive supplies of the needed factors. (3) There is reason to believe that other factors, possibly members of the B complex, are involved in the integrity of nerve tissue. Therapy of neuropathy should therefore include all of these substances.

The neuropathy of diabetes mellitus is a complicated disturbance which almost certainly involves a deep-seated metabolic defect. It may affect the tissues of either the central or the peripheral nervous system, and it may actually become worse after regulation of the diabetic state to reasonably good metabolic balance. Because it is so poorly understood, physicians are at a loss to know how it should be treated most intelligently. Evidence for a deficiency factor in its pathogenesis is strong and whole vitamin supplements rather than thiamine alone are indicated, but results of treatment are uniformly disappointing.

Miscellaneous.—Rapid relief of pain in herpes zoster was noted from use of thiamine in large doses, usually given by injection. Since this disease is due to an infection of the nerve root and appears to be unassociated with any nutritional problem, this therapy hardly seems justified. Further extensive corroboration is necessary before this claim can be accepted.

The neurologic manifestations of pernicious anemia may respond slightly to the administration of thiamine. Reports are conflicting on this point, and because of experimental evidence of the importance of other B factors in maintaining normal nutrition for nerve tissue, it would seem to be more logical to give the whole B complex in pernicious anemia.

The difficult question as to the relationship of thiamine and the other B factors to resistance to infection has been completely and critically reviewed by Perla. His conclusions are based on a great many careful observations in both experimental animals and man. There is some dependable evidence that B complex avitaminosis is associated with a general lowering of resistance to infection. The mechanism of this effect is possibly through its influence on the production of certain antibodies and through interference in other ways with oxidation-reduction processes in metabolism. Such observations provide a rational basis for directing attention to the nutritional status of individuals with a general failure to resist infections of all types. General inanition is inseparably bound to this entire problem, and an important loss of immunologic resistance to infection can be clearly correlated with inadequate protein intake, as discussed in the section on Proteins.

Study of the vitamin literature reveals that thiamine has been used in the treatment of an almost unbelievable variety of conditions. A few are: Korsakoff's syndrome, delirium tremens, postirradiation nausea, trigeminal neuralgia, multiple sclerosis, sci-

atica, rheumatoid arthritis, sacro-iliac arthritis, diabetes mellitus, morphine addiction and nerve deafness. The vitamin has been given by every route, including the intrathecal. It is perhaps too early to pass final judgment on any of these considerations, but it is probable that in most of these diseases the use of thiamine supplements will eventually be found to be unwarranted, particularly if there is no concomitant dietary insufficency. Especial mention should be made, however, of Korsakoff's syndrome in which, as in alcoholic polyneuritis, the condition appears to be due not specifically to the toxic effects of alcohol but rather to a coexistent nutritional deficiency. It is hoped that further intensive study, as well as the added perspective of time, will decide these questions.

Diagnostic Methods

Although the fundamental basis for diagnosis of most deficiency diseases remains the history and physical examination, there is a growing interest in the use of laboratory methods, chemical and otherwise, to assist in the identification of mild and latent deficiency disease. Exhaustive search has been made for a dependable chemical method for the diagnosis of thiamine deficiency, applicable to mild as well as to severe cases, and several technics appear promising. Three analytical procedures have been successfully applied to urine—the colorimetric, the thiochrome (fluorescent) and the yeast fermentation methods—all of which have consistently demonstrated that the urinary excretion of thiamine is a good

index of the nutritional status of human beings. Excreted thiamine is thought by some to represent the extracellular fraction of the vitamin which, under most conditions, may be expected to be in equilibrium with the intracellular portion to serve a biochemical function in metabolism.

In one such study (Williams and Mason) the excretion of thiamine by normal subjects exceeded 100 micrograms daily, and 20 per cent or more of a test dose of 1 mg. administered subcutaneously was excreted within one hour. Excretion by deficient subjects fell below this line, thereby providing a means for sharp differentiation between normal and pathologic individuals. Employing a slightly different technic, another group (Melnick, Field and Robinson) found the basal excretion of deficient subjects to fall below 60 micrograms daily and 9 per cent or less excretion within four hours of a test dose of 350 micrograms per square meter of body surface, administered intramuscularly.

As mentioned previously, the measurement of bisulfite-binding substance or pyruvic acid specifically has not been successfully applied in early or mild thiamine deficiency. However, one group of investigators (Bueding, Wortis) has demonstrated a higher rise of blood pyruvate in deficient than in normal subjects following the ingestion of glucose under fasting conditions. The average normal fasting level was 0.98 mg., and the postglucose rise averaged 0.48 mg. These figures were exceeded in the deficient cases.

Another group (Robinson, Shelton and Smith) has

pointed out that diabetic-like glucose tolerance curves, especially when they return to normal levels within three hours, are usually due to malnutrition. These workers believe that marginal malnutrition can frequently be recognized by this means.

It is obvious that accurate laboratory diagnosis of deficiency states is still out of reach of most laboratories. Such excellent progress has been made within the past few years, however, that it is reasonable to hope for much more in the future.

Therapy of Thiamine Deficiency

Thiamine is readily absorbed from the gastro-intestinal tract, and for this reason it can usually be effectively administered by mouth. This general principle obviously will not hold in any clinical condition in which absorption from the intestine is known to be impaired, owing to a pathologic process involving the mucosa, increased intestinal rate or any other reason. Under these circumstances it can be administered parenterally, either subcutaneously, intramuscularly or intravenously, in the form of sterile solutions. It is rarely if ever necessary to give thiamine by the intravenous route, however, for reasons which will be discussed.

The daily requirement of this vitamin for normal healthy adults is now known to be about 1-2 mg., or 330-660 I.U., and the normal capacity for storage is not large. These two factors are of great importance in anticipating the fate of any dose of thiamine used in therapy. It seems almost certain that dosage

formerly was often excessively high and out of all proportion to the capacity of the organism to utilize and store the material. It is almost self-evident that no value can be derived from active material which is excreted in the urine within the first few hours after administration. On the other hand, it is well recognized that if chronic deficiency states with degenerative tissue changes are to be corrected, doses many times the maintenance level must be given for prolonged periods regardless of the losses through excretion.

Much work has been done in an attempt to establish with greater accuracy the daily human thiamine requirements. In one study,[11] performance was as satisfactory on an intake of 0.23 mg. per 1,000 calories as on one of 0.63 mg. In another investigation,[12] a daily intake of 0.47 mg. per 1,000 calories was found to be the minimal requirement. In a third,[13] 0.44 mg. per 1,000 calories was the minimal requirement. The National Research Council recommends 1.5 mg. daily for a moderately active man.

All of the data given previously concerning human requirements and urinary excretion serve to emphasize the adequacy of moderate doses and the lack of need for excessively large doses (50-1,000 mg.) over short periods of time, particularly when it is injected. The only exceptions to the general rule which seem justified at present are those instances in which some pharmacologic action of thiamine is

[11] Keys *et al.*, op. cit.
[12] Holt, op. cit.
[13] Alexander, B., and Landwehr, G.: J. Clin. Investigation, 25:287, 1946.

suspected. No such effects have been proved up to the present time. For these reasons, it seems wise to emphasize that not even under conditions of the most marked thiamine deficiency does the dose need to exceed 25-30 mg. daily, and for most conditions 10 mg. daily is an abundant supply, to be continued as long as evidences of deficiency exist. The dose may be reduced somewhat, to 10 or even 5 mg. daily, after the first few weeks. The Council on Foods and Nutrition of the American Medical Association officially recommends doses of 10-20 mg. twice daily until relief of symptoms in acute deficiency states and 5-10 mg. twice daily for indefinite periods in chronic conditions. Distinction should be made between the improvement of suboptimal intake, for which a 1-3 mg. supplement daily is adequate, and true deficiency states with tissue as well as biochemical changes, for which larger dosages are required for prolonged periods.

When excessively large doses are given, the greater part is promptly excreted, for the kidney appears to eliminate the excess faster than it can be stored. For this reason it would seem that a greater effect might be achieved by giving several smaller divided doses during the day than by giving one large dose. It should be stressed again that there is no evidence that thiamine has any therapeutic effect except as it restores reserves depleted in deficiency states. The study of Alexander and Landwehr[13] provides evidence that in no circumstance are doses above 35 mg. daily justified.

Based on these considerations, the treatment for *beriberi* in its most severe form should include thia-

mine supplements to the diet in doses of 10 to 35 mg. daily, given by mouth if there is no nausea, vomiting or diarrhea and by subcutaneous or intramuscular injection if the condition of the gastro-intestinal tract interferes with absorption. In either case it is better to give at least three divided doses of 5 to 10 mg. daily. It should be emphasized in this connection that the dosages here recommended are one-fifth to one-tenth those which have previously been suggested. While there is no contraindication to the larger amounts, the most recent critical work on thiamine excretion seems to support the smaller supplements. As the clinical manifestations begin to recede, this dosage may be reduced to 8-10 mg. daily and eventually to a maintenance level of 1 to 2 mg. daily. Because of the multiple deficiencies which make up the clinical condition of beriberi, additional vitamin supplements must also be given. The nerve lesions clear very slowly. The oral lesions and diarrhea are most closely related to a lack of the pellagra-preventive factor. Nicotinic acid in divided doses totaling 300-500 mg. daily can be given by any route which seems indicated. Riboflavin, vitamin B_6 and the other members of the complex as well as ascorbic acid and the various fat-soluble factors must also be added by the appropriate supplements.

Therapy for *polyneuropathy* should be the same regardless of its etiology, which may be infectious, "toxic," "cachectic," "alcoholic," diabetic, metabolic or gestational. In severe form, the therapeutic measures may be conveniently subdivided as follows:

1. Replacement of fluids and salt. In any patient who has been vomiting for a prolonged period, a state of dehydration and hemoconcentration is to be expected, which can be relieved by the parenteral administration of fluids in adequate amounts. This should be in the form of physiologic saline solution and can be given by either the subcutaneous or the intravenous route. The quantity of fluid needed cannot be arbitrarily stated but is best judged by the urinary output, which should not be less than 1 L. daily. If this represents one half to two thirds of the daily intake, then approximately 2 L. will be needed every 24 hours, often for many successive days. Hemoconcentration may mask deficiencies by causing values for various blood constituents to fall within normal limits. As the dehydration is corrected, signs of hemoconcentration should disappear.

2. Replacement of protein. The edema common to many forms of this condition is often, although not always, due to hypoproteinemia. Protein is best administered by mouth, but when this is impossible owing to nausea and vomiting, it must be given either by transfusion of whole blood or plasma or by the new and as yet not completely satisfactory intravenous use of amino-acids derived from casein digests. It is well known that serum protein values are raised very slowly by transfusion; furthermore, it is not wise to use whole blood when the patient's red cell count and hemoglobin values are normal. When administered by mouth, the proteins of most value in restoring plasma levels are casein and liver.

3. Administration of carbohydrate. Patients who have been vomiting usually have marked ketosis if not frank acidosis. This is due to several factors, but chiefly to the depletion of carbohydrate reserves from inadequate intake of food and the attendant necessity for the utilization of fat as a source of fuel. The resulting ketone bodies are present in the urine, and acetone is readily detected on the breath. An adequate supply of glucose will promptly remove this ketosis. Glucose is most conveniently supplied by intravenous injection or hypodermoclysis of a 5 per cent solution until food is tolerated by mouth. One liter of 5 per cent glucose solution will supply 50 Gm. carbohydrate in the form of an isotonic preparation which can be mixed with an equal volume of normal saline. Usually 50-60 Gm. is an adequate carbohydrate intake by this route. It should be emphasized that for the reasons already mentioned, the administration of carbohydrate will aggravate any thiamine deficiency which may exist in latent form.

4. Administration of vitamin supplements. Thiamine can be given by any of the parenteral routes in 20 to 35 mg. doses. That these doses are adequate is indicated by the prompt excretion of the greater part of the daily dose in the urine on the second or third day of treatment in this condition. Clinical improvement parallels this finding. Other vitamin supplements are also necessary, including riboflavin, nicotinic acid, the other members of the B complex, ascorbic acid, vitamin B and vitamin E, details of which are discussed in appropriate chapters.

Although several other nutritional supplements are needed to make the intake complete, such as calcium, iron, vitamin A and vitamin D, these other deficiencies are not as critical as those previously mentioned and therefore can usually await the return of normal gastro-intestinal function. It should be unnecessary to mention that feeding by mouth should be started carefully and in small frequent feedings as soon as they can be tolerated.

In less severe cases and in patients who are not acutely ill, many of the aforementioned measures are unnecessary. It is often possible to reestablish normal nutrition by simple administration of the proper supplements until proper diet makes their use superfluous. Hyperemesis gravidarum may present special problems because of the extra demands of pregnancy, but as far as its nutritional aspects are concerned, the appropriate measures are identical to those recommended for other forms of thiamine and B complex deficiency.

RIBOFLAVIN

The deficiency condition produced in rats by Goldberger and Lillie in the course of their experiments relating to the cause of pellagra was characterized by patchy or complete loss of hair, by an ophthalmia which led to the development of cataracts and by failure of the animals to grow. These were considered typical manifestations of the lack of vitamin B_2 or G (named by the British and American investigators, respectively). For several years certain inconsistencies were noted in the appearance of these lesions which were not understood. Studies by Hogan and Hunter in 1928 finally disclosed that these inconsistencies were due to the fact that vitamin B_2 really consisted of more than one factor, one of which was a pigment; consequently the experimental picture produced was revealed as a multiple deficiency disease. Destruction of the pigment by ultraviolet irradiation eventually led to recognition of the identity of the factor responsible for these manifestations in rats with the water-soluble yellowish-green fluorescent pigment known since about 1879 to be present in milk. By 1933, an exact parallelism was shown to exist between the capacity of certain growth factors to supplement the G-deficient diet devised by Bourquin and Sherman two years earlier and the intensities of yel-

low pigmentation of these preparations. The factor in question was first named lactoflavin, because of its earlier isolation from milk, and finally riboflavin as soon as the structure was known and the synthetic compound was found to have the same potency as the naturally occurring vitamin. In April, 1937, the suggestion of the Council on Pharmacy and Chemistry of the American Medical Association that vitamin B_2, or G, be officially known as riboflavin was accepted by the Committee on Vitamin Nomenclature and the American Society of Biological Chemists, so that the official name of this factor henceforth need not involve the B nomenclature.

The history and chemistry of riboflavin are inseparably bound to the history of the yellow oxidation enzyme discovered by Warburg and Christian in 1932. This compound was known to be one of high molecular weight, probably containing a protein, and was also demonstrated to be of the most fundamental importance in biologic oxidations. Since the early days of its investigation, it has been isolated from a great variety of sources including yeast, eggs, plant materials, liver, kidney, heart muscle, skeletal muscle and urine. A fascinating chapter in biologic research and medical history has been written by the brilliant investigators who have established the relationship of riboflavin to living oxidation systems through the intermediate activity of the yellow enzyme.

The structures of these two materials are shown in Figures 12 and 13. It will be noted that the yellow enzyme contains, in addition to protein and the ribo-

flavin portion, a molecule of phosphoric acid through which the protein bond is established. So far as is known, this vitamin is active in biologic systems only to the extent that the organism is able to carry out synthesis of the yellow enzyme from the constituent materials. The unusual and serious nature of the

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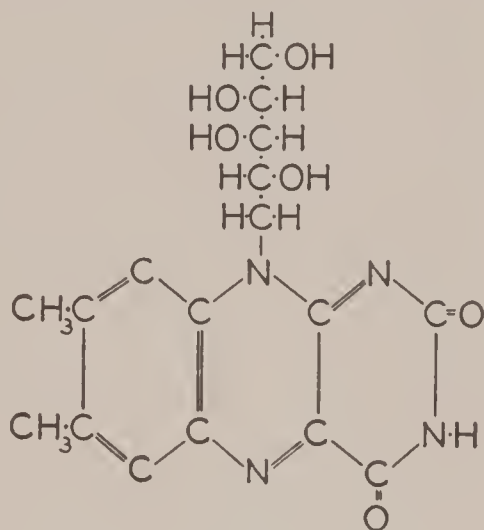
Fig. 12.—Riboflavin.

manifestations of severe riboflavin deficiency in animals may well be due to the key position occupied by this enzyme in life processes.

Biologic oxidations are best thought of as processes in which hydrogen is removed from the metabolite to be burned. This hydrogen, often removed only with difficulty by strong reagents in the test tube, is rendered labile and easily available by means of enzyme activity. The yellow enzyme, similar to other oxidation enzymes, has the remarkable and indispensable ability to be alternately oxidized and reduced, that is to say, alternately to give off and to take on an atom of hydrogen. This hydrogen is received from

the metabolite to be burned, either directly or through the intermediate activity of other similar enzymes, and is then passed on either directly to molecular oxygen or again through a chain of enzymes to oxygen, to form hydrogen peroxide which is then decom-
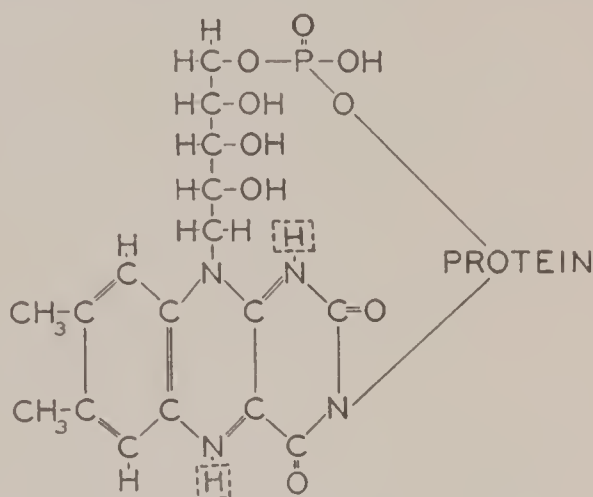
Fig. 13.—Warburg's yellow enzyme.

posed by special mechanisms to form water and molecular oxygen. It is noteworthy that according to present concepts all biologic oxidations by which heat and energy are released in animals take place through mechanisms of this general type. Riboflavin, as the active part of the yellow enzyme, occupies an important key position in this scheme, and from the chemical standpoint it can be considered as a hydrogen carrier. The labile hydrogen which is alternately added and removed is marked with dotted lines in the formula.

The original enzyme of Warburg and Christian has now come to be designated as the "old yellow enzyme." Since 1938 biochemists have discovered many more

flavin-containing enzymes which are of vital importance in biologic oxidations. Nine have been clearly identified, grouped together under the general classification of "flavoproteins." They are concerned with the oxidation of such important compounds as fumaric and succinic acids, various aldehydes, cytochrome C and the purines. It is probable that several more flavoproteins will be added to the present list. Their abundance in the liver runs parallel to its high content in riboflavin and emphasizes the complex biochemical activity of that organ. The content of these enzymes in the liver has been found to be diminished in riboflavin deficiency.[1]

Occurrence

Riboflavin is abundant in Nature. As already stated, its concentration is greatest in milk, eggs, liver, muscle and yeast. Table 6 shows its incidence in many commonly used foods, including the best sources. Biosynthesis in the human intestine is probably insignificant.

In many natural sources, this vitamin occurs in combination with phosphoric acid as an ester. So far as is known, the uncombined or free form must be changed into the phosphoric ester before it becomes biologically active. This is thought to occur in the intestine, probably during the process of absorption.

Riboflavin is a thermostable factor which readily withstands the heat of ordinary types of cooking, particularly when the medium is acid. It is, however,

[1] Axelrod, A. E., and Elvehjem, C. A.: J. Biol. Chem., 140:725, 1941.

TABLE 6.—RIBOFLAVIN CONTENT OF FOODS*

	MG. PER 100 GM.
Apples	0.02
Bananas	0.06
Carrots	0.06
Cheese	0.52
Eggs	0.34
Milk, whole	0.17
Oranges	0.03
Potatoes	0.04
Spinach	0.24
Tomatoes	0.04
Turnips	0.06
Whole wheat flour	0.12
Yeast, brewers'	5.45
Yeast, bakers'	2.07
Beef, roast	0.15
Hamburger	0.13
Lamb, leg	0.26
Liver	2.80
Heart	0.90
Ham	0.19
Pork loin	0.18
Poultry	0.18
Liver sausage	1.12

* These figures are from Tables of Food Composition prepared by the Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, in co-operation with the National Research Council, Miscellaneous Publication no. 572 (1945). Nutritive values are given for foods as brought into the house for consumption; no account has been taken of losses of food value that may occur in preparation of meals.

rather sensitive to alkali, as it is to daylight, both of which agents cause irreversible transformation. In general, it may be stated that roasting and baking meats tends to destroy the largest percentages of flavin, amounting in some instances to 60 per cent. Frying of meat is somewhat less destructive of the flavin content, while stewing produces almost no change.

Because of the importance of milk as a dietary source of riboflavin (1 qt. contains 1.2-3.5 mg.) the losses on exposure to light are important. Boiling for 45 minutes in the dark causes no appreciable loss. In reasonable daylight without exposure to the sun there is 26 per

cent loss after five minutes, 39 per cent loss after 15 minutes, and 48 and 64 per cent after 30 and 45 minutes, respectively.[2] An even greater loss has been noted in milk left standing in sunshine on the doorstep; Ziegler[3] reported losses of from 54 to 68 per cent on two hours of such exposure. Destruction by pasteurization is only 9-16 per cent and by irradiation procedures to increase vitamin D potency, only 5-8 per cent.[4] Thus the greatest hazard lies in exposure to sunshine on the doorstep after delivery.

Thorough investigation of the daily human requirement for riboflavin has led to gradual downward revision of earlier figures. One of the best studies[5] set 0.5 mg. per 1,000 calories as the amount necessary to maintain normal tissue levels. Another[6] established 0.5 mg. per 1,000 calories as the requirement for children of preschool age. Including some of the earlier investigations, the requirement for adults has been variously estimated to be between 1.5 and 3 mg. daily. It is probably nearer 3 mg. on the basis of excretion studies. The Committee on Foods and Nutrition of the National Research Council has accepted a daily allowance of 2.7 mg. for a moderately active man as the required intake. Because of the tenacity with which the body holds on to its supply of this material, deficiencies develop slowly, and even at death experimental

[2] Williams, R. J., and Cheldelin, V. H.: Science, 96:22, 1942.
[3] Ziegler, J. A.: J. Am. Chem. Soc., 66:1039, 1944.
[4] Ziegler, J. A., and Keevil, N. B.: J. Biol. Chem., 155:605, 1944.
[5] Williams, R. D.; Mason, H. L.; Cusick, P. L., and Wilder, R. M.: J. Nutrition, 25:361, 1943.
[6] Oldham, H.; Johnston, F. A.; Kleiger, S., and Hedderich-Arismendi, H.: J. Nutrition, 27:435, 1944.

animals show appreciable amounts of flavin in the heart, liver and kidneys. In this respect riboflavin is apparently conserved more rigorously than is thiamine. Urinary excretion, which in normal healthy adults amounts to 800-1,200 µg., falls promptly with inadequate intake, thereby providing a possible method for identification of deficiency states. Hagedorn and his associates[7] studied a group of men subsisting on a standard diet with a variable intake of riboflavin and found riboflavin excretion rates of 0.05-2.4 mg. per 24 hours. The larger figures were invariably associated with a high intake, either from large amounts of milk or from vitamin supplements.

Riboflavin Deficiency

There are only two types of lesions which so far have been fairly well established as being due to a specific lack of riboflavin. Sebrell and Butler were the first to recognize this deficiency in a condition which they named cheilitis, occurring in pellagrins and apparently caused by a deficiency of some factor other than nicotinic acid. These observations have since been confirmed many times, and the lesions are now known to occur with moderate frequency unassociated with pellagra. Their regular occurrence in that disease, however, points to multiple rather than to simple deficiency etiology for pellagra.

The lesions occur on the lips, along the mucocutaneous border and particularly in the corners of the mouth. They consist of redness, desquamation and

[7] Hagedorn, D. R.; Kynos, E. D.; Germek, O. A., and Sevringhaus, E. L.: J. Nutrition, 29:179, 1945.
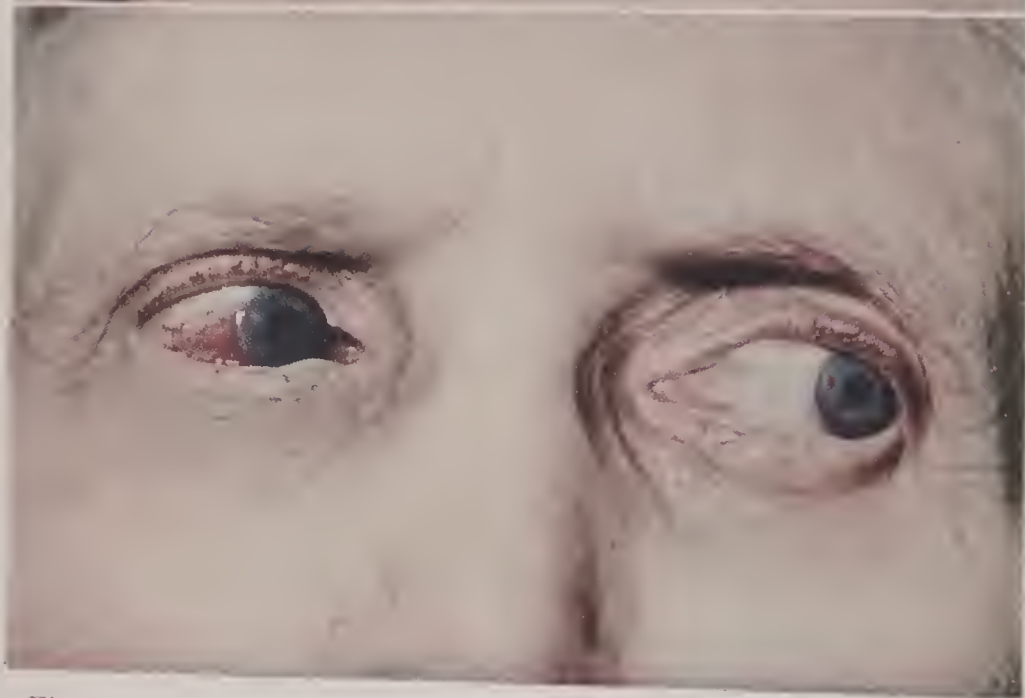
Fig. 14 (above).—Pitted lesions near mucocutaneous border of lips result from small ulcerations which do not completely heal. Cracks radiating from corners of mouth likewise heal only with specific vitamin therapy, and may leave scarring in the form of rhagades. (Reproduced by courtesy of Dr. Henry Field, Univ. of Michigan, and Dr. A. G. MacLeod, Upjohn Co., Kalamazoo, Mich.)

Fig. 15 (below).—Injection of conjunctival vessels clearly visible. Change most marked around sclerocorneal junction; it clears with administration of riboflavin in adequate amounts. Rosacea keratitis often associated with lesions of acne rosacea.

finally ulceration at these sites. The appearance of fissures at the corners of the mouth leads to rhagades formation and in severe cases to permanent scarring. This condition has been described as marginal stomatitis and as perlèche. The latter term, however, applies also to a lesion now recognized as being due not to ariboflavinosis but to the growth of a fungus in the corners of the mouth secondary to the drooling of saliva, usually from ill-fitting dentures. Thus the lesion is not specific for riboflavin deficiency, and vitamin therapy will be of help only when it is directly associated with such deficiency. There is often associated with the lip lesions an oily desquamation around the nose, in the nasolabial fold and on the ears. A filiform lesion commonly called shark-skin dermatitis associated with a deposit resembling urea frost has been thought to be a more advanced stage of this same condition. In addition, some patients have given a history of visual disturbances, lacrimation and failing vision; this may be associated with intense bulbar conjunctivitis which causes severe burning sensations.

It is noteworthy that cure of these same lesions, recognized as cheilitis, has recently been reported by the use of pure crystalline vitamin B_6 parenterally in doses of 20 to 50 mg. daily. Healing of the lesions is apparently much more rapid with this preparation than usually occurs when riboflavin is used. Equally satisfactory results have been obtained also by using nicotinic acid and ascorbic acid in ordinary therapeutic dosage. The explanation for these interesting observations is not clear, but they may indicate that

cheilitis is caused by a multiple nutritional deficiency.

The second type of lesion attributable to riboflavin deficiency involves the eye. Sydenstricker and his associates studied 47 patients with dietary insufficiency and found unmistakable evidence of pathologic changes in the cornea and surrounding structures which responded rapidly and satisfactorily to the administration of riboflavin. In many of these patients, typical lesions of cheilitis were also present, but in others there were no other deficiency manifestations. The lesions consist of an unusual vascularization of the limbus or sclerocorneal junction, with fine filaments growing out toward the center of the cornea. This plexus of vessels, studied properly only with the slit lamp, was found always to be on the anterior surface in contradistinction to that of syphilis, which is always posterior. A clouding of the cornea caused by nebulas, both anterior and interstitial, was a common finding. Associated with these changes was a tendency to marked mydriasis and to pigmented spots on the anterior surface of the iris. Subjective complaints consisted of photophobia, burning and smarting of the eyes, visual fatigue, loss of visual acuity which could not be accounted for by refractive error, lacrimation and blepharospasm.

Doubt has been cast on the specificity of these lesions by the observation of similar changes in conditions unrelated to malnutrition. Ophthalmologists especially have refused to accept a single etiologic factor. It should be pointed out that the plexus of vessels must actually encroach on the cornea and that they should represent new growth of capillaries rather than simple

fulness of the limbus vessels. Such changes should be present bilaterally and around the entire circumference of the cornea if they are to represent true deficiency lesions. Mann[8] summarized these findings from the point of view of the ophthalmologist. Spies and his associates[9] reviewed 500 carefully studied cases and re-emphasized the nonspecificity of the lesions. They concluded that the response to riboflavin administration is the best diagnostic criterion.

Interest has been expressed in the possible rôle of riboflavin in the prevention of cataract. This is due largely to the common occurrence of cataract as a part of deficiency of this factor in rats and production of a similar lesion in pigs. But despite repeated demonstration of this relationship in animals, there have been no conclusive clinical results.

The explanation for the vascular changes in the cornea probably lies in interference—owing to a lack of available riboflavin—with the normal respiration of corneal cells and a compensatory attempt by the cornea to improve its blood supply. Therapy often results in complete regression of all changes, including the corneal opacity, although the plexus of vessels, emptied of blood, may be visible with a slit lamp for long periods after therapy is instituted.

The same lesion of the cornea also was observed by Johnson and Eckardt, but they noted, in addition, frequent association of the lesions of acne rosacea.

[8] Mann, I.: Am. J. Ophth., 28:243, 1945.

[9] Spies, T. D.; Perry, D. L.; Cogswell, R. C., and Frommeyer, W. B.: J. Lab. & Clin. Med., 30:751, 1945.

They designated the eye condition as rosacea keratitis and reported brilliant therapeutic results in both lesions from the administration of riboflavin in divided doses, not exceeding a total of 5 mg. daily.

These various manifestations have been cleared up quite satisfactorily by the use of riboflavin supplements to the diet. For the eye lesions adequate dosage usually does not exceed 15 mg. daily administered orally. Daily doses of 2.5-50 mg. by mouth have been given with profit in acute deficiencies; the lower figure probably is closer to the required supplementing dose, even in advanced deficiency states. The Council on Foods and Nutrition of the American Medical Association recommends 5 mg. three times daily for several weeks in acute cases, and 3-5 mg. daily for indefinite periods in chronic cases. The speed with which riboflavin stores are returned to normal in severe deficiency states is striking, as shown by a rise in urinary excretion and subjective improvement. The saturation point has been observed as early as the third day after a daily oral dose of only 5 mg.

The responsibility of flavin deficiency for the central and peripheral nervous system changes in beriberi and pellagra has been suspected, since it has been demonstrated in both animals and humans that thiamine does not restore to normal these structural changes in nerve tissue. These suspicions have been further substantiated by the production of nervous system lesions in pigs on diets deficient in riboflavin.[10] The animals de-

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[10] Wintrobe, M. M.; Buschke, W.; Follis, R. H., Jr., and Humphreys, S.: Bull. Johns Hopkins Hosp., **75**:102, 1944.

Fig. 16.—Section through sciatic nerve of chick on diet deficient only in riboflavin. Nerve degeneration stains black. (Courtesy of Dr. Paul Phillips, Dept. of Biochemistry, Univ. of Wisconsin.)

veloped a stiff, mincing, hesitant gait. In the therapy of human peripheral neuritis, thiamine alone has often given disappointing results, and although the evidence is far from clear it seems wise to recommend the use of whole B complex preparations. Much more study is necessary to clarify the situation. Figure 16 shows the peripheral nerve lesion in chicks.

A special type of glossitis characterized by a magenta color and flattening of the papillae was ascribed to riboflavin deficiency by Kruse, Sydenstricker, Sebrell and Cleckley in 1940. Fatty degeneration of the liver has been attributed to the same cause. These observations have not been finally evaluated, but it is probable that the latter is actually a lesion of choline deficiency. Riboflavin has also been used in the treatment of anorexia, baldness, pemphigus, conjunctivitis and a variety of other conditions, but there is little or no evidence to justify its use.

As chemical and microbiologic methods for the estimation of riboflavin in biologic materials have been devised and improved, guesswork and empiricism have gradually been eliminated regarding the relationship of riboflavin to human nutrition. Using one of the best of these methods (the microbiologic technic of Strong et al.), a 24 hour urinary excretion of less than 500 µg. should be considered low; subjects with obvious clinical deficiency manifestations frequently excrete less than 50 µg. daily. Further work to make these technics easier and to widen their application will go far toward throwing further light on this entire subject.

NICOTINIC ACID—NIACIN

Although the existence of nicotinic acid has been known since 1867 and its occurrence in biologic material was first recognized in 1912, no special significance was attached to it until 1937, when Elvehjem and his associates reported that nicotinic acid amide present in liver would cure blacktongue in dogs. Since this canine disease had long been considered the counterpart of human pellagra, the importance of this substance in human nutrition was soon established.

The important fundamental work of Goldberger and his co-workers, beginning in 1922, established pellagra as a deficiency disease, after the condition had been known for several centuries (1762) without any definite etiology having been assigned to it. These investigators also demonstrated the efficacy of liver in curing the lesions, but the exact factor in the liver responsible for this effect remained unknown until 1938. The names "niacin" for nicotinic acid and "niacinamide" for nicotinic acid amide have been accepted as official by the Council on Foods of the American Medical Association and by the American Institute of Nutrition.

The mechanism of action of nicotinic acid in biologic systems has been partially elucidated through investigations of the chemistry of fermentation. The

heat-stable substance necessary for fermentation has been named cozymase to indicate its action with the heat-labile enzyme, zymase. The structures of nicotinic acid and of cozymase, or coenzyme, are shown in Figures 17 and 18.

Both coenzymes I and II, or diphosphopyridine nucleotide and triphosphopyridine nucleotide, respectively, are involved in different ways in carbohydrate metabolism in animals, as they are important in the fermentation of carbohydrates by yeast. These substances are thought to act in a manner similar to that of riboflavin, through their capacity to take on and give off an atom of hydrogen under certain circumstances. In this way they act as hydrogen carriers, assisting in the transport of hydrogen from the metabolite to be burned through a series of steps to molecular oxygen where water is

Fig. 17.—Nicotinic acid amide.

eventually formed. The labile hydrogen is shown in the formulas by dotted lines. Thus, these compounds are of vital importance in biologic oxidations, and it is logical to anticipate the appearance of serious metabolic defects in the absence of adequate nicotinic acid from which these coenzymes are synthesized by the body. So far as is known, coenzyme occurs almost universally in the tissues of animals, the concentration tending to vary with the rate and intensity of oxidative metabolism taking place in any particular organ. In the blood, it is present entirely in the red blood
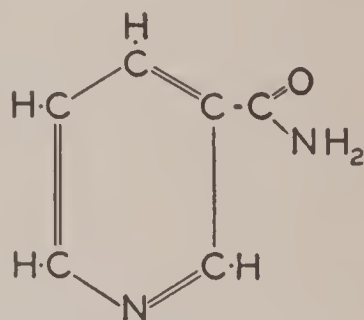
cells, and its concentration is remarkably constant, even in serious deficiency states. In muscle, liver, heart and brain, the concentrations tend to fall gradually as the deficiency progresses.

The abundance of nicotinic acid in natural sources is comparable to that of the other members of the B
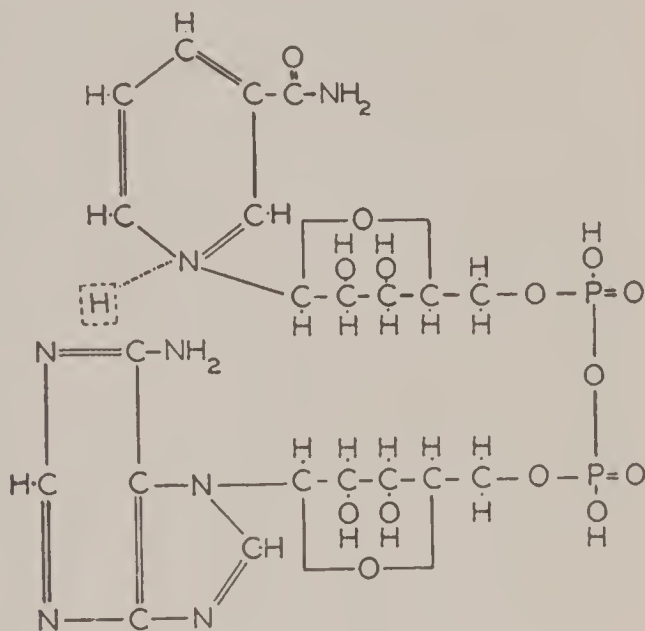
Fig. 18.—Coenzyme.

complex. In human diets, the most valuable supplies are again found in cereal grains, yeast and animal tissues. Table 7 gives the amounts of nicotinic acid found in a variety of foods.

\ The daily human requirement of nicotinic acid has been estimated at amounts ranging from 5 to 25 mg. The Council on Foods and Nutrition of the American Medical Association has accepted the range of 11 to 20 mg. daily for adults, males requiring in general more than females, with the recommended intakes graded according to physical activity. Recent careful

quantitative work establishes 0.15 mg. per Kg. of body weight as the "protective" dose. On this basis, a man weighing 70 Kg. (155 lb.) would require 10.5 mg. daily. An optimal dose would, of course, be higher.

TABLE 7.—NICOTINIC ACID CONTENT OF FOOD*

	MG. PER 100 GM.
Beef	5.1
Liver	16.1
Yeast, brewers'	36.2
Yeast, bakers'	28.2
Pork, loin	3.8
Ham	4.1
Tongue, beef	5.0
Veal	6.5
Heart	6.8
Skim milk powder	1.1
Wheat germ	4.6
Corn, yellow	1.4
Corn meal, refined white	0.9
Corn meal, yellow whole-grained	2.1
Rice, white	1.4
Rice, brown	4.6
Whole wheat flour	5.6
Wheat flour, white, enriched	3.5
Barley cereal	3.1
Oatmeal	1.1
Dried peaches	5.4
Peanuts	16.2
Peanut butter	16.2
Tuna fish, canned	10.6

* These figures are from Tables of Food Composition prepared by the Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, in co-operation with the National Research Council, Miscellaneous Publication no. 572 (1945). Nutritive values are given for foods as brought into the house for consumption; no account has been taken of losses of food value that may occur in preparation of meals.

According to Aykroyd and Swaminatham,[1] 5 mg. daily seems to be adequate for rice-eating humans, whereas maize-eaters may develop pellagra on a somewhat higher daily intake. Thus other factors in the diet may condition the requirements for niacin.

Nicotinic acid is one of the most thermostable mem-

[1] Aykroyd, W. R., and Swaminatham, M.: Indian J. M. Research, 27:667, 1940.

bers of the B complex, and it may be rendered bacteriologically sterile by autoclaving without any appreciable destruction. Thus, the danger of loss from ordinary methods of cooking is slight. As indicated by its chemical structure, it acts as a weak acid and readily forms sodium and potassium salts which, in solution, have mild alkaline reactions. There is good evidence that it is synthesized in significant amounts in the intestine by the normal bacterial flora, for excretion can be shown to exceed intake under experimental conditions. This fact may have considerable significance in any consideration of the requirements for normal nutrition in all species, including man.

Pellagra is an endemic disease in certain sections of the United States and in other continents. With a few exceptions its incidence is closely correlated with the economic status of the population and therefore with the diet. It has been in the past responsible for a serious degree of illness and suffering among the poorer sections of both Negroes and whites in the southern states, where the diet consists chiefly of the three staple foods, molasses, salt pork and corn meal.

The incidence of this disease when corn is an important item of diet has been noted for many years, but its significance has not been understood until recently. A series of investigations have now related it to the niacin content. Specifically, the important factor appears to be tryptophan, an amino-acid, known to be present in very small amounts in corn. Krehl et al.[2]

2 Krehl, W. A.; Sarma, P. S.; Teply, L. J., and Elvehjem, C. A.: J. Nutrition, 31:85, 1946.

showed that in rats the addition of 0.05 per cent of tryptophan to the diet prevented the effect of corn and also were able to reproduce the corn effect with other diets low in tryptophan. A similar relationship was demonstrated in young pigs by Wintrobe and his co-workers.[3] It is probable that the same mechanism exists in humans and accounts for the natural occurrence of pellagra. Tryptophan may act through its support of bacterial growth in the intestine, with attendant nicotinic acid synthesis, as suggested by the Wisconsin investigators.

Pellagra occurs at all ages and is frequently seen in infants and children in the endemic areas. Its appearance in infants, always related to a dietary deficiency in the mother, is of particular importance because the manifestations are not characteristic. The condition is usually latent but responds nevertheless to the administration of nicotinic acid.

In addition to endemic pellagra in which the incidence is related to the dietary habits of the population in certain regions, the disease also occurs commonly in alcoholics. Stomatitis and glossitis have been reported in 60 per cent of all chronic alcoholics. The mechanism of occurrence of pellagra under these circumstances is similar to that of beriberi. Indeed, the two conditions are often present together, when they represent a serious B complex deficiency. Here again, as in endemic pellagra among corn-eaters, a low intake of protein may be a related etiologic factor.

[3] Wintrobe, M. M.; Stein, H. J.; Follis, R. H., and Humphreys, S.: J. Nutrition, 30:395, 1945.

The clinical picture of pellagra is a characteristic one which obviously may exist in any degree of severity. The presenting complaint is often referable to the gastro-intestinal tract and may consist of sore tongue, gums or mouth, loss of appetite, nausea and vomiting, abdominal pain or diarrhea. However, the complaints may involve almost any part of the body. Insomnia, loss of weight and strength, burning sensations all over the body, headache, nervousness, mental depression, irritability, apprehension and confusion are all common symptoms. In the later stages of the disease, the mental picture may be one of profound dementia, which is completely cured by therapy if the disturbance has not been present for too long a time.

Seven types of epithelial lesions have been described in pellagra: (1) dermatitis on exposed surfaces; (2) dermatitis in areas of trauma; (3) thickening and pigmentation over the bony prominences; (4) perineal and genital lesions; (5) sebaceous gland changes on the face; (6) lesions of the lips and mucocutaneous surfaces at the corners of the mouth, and (7) changes in the superficial structures of the eye. The first of these is considered to be the most characteristic of all pellagrous skin changes. They are usually symmetrical and their cause appears to be related to ultraviolet irradiation. The lesions are most common on the hands, wrists, elbows, face, neck, knees, feet and perineum. These skin areas first become slightly reddened and itch and burn intensely. They next become tense and swollen, the redness increases and at times

the skin cracks and ulcerations appear. Skin atrophy follows, during which the color fades to brown, the skin surface becomes extremely rough, and desquamation and cracking are present, often to the extent of bleeding. It is from these skin lesions that the disease derived its name. The second type is seen in such areas as the ring finger under a wedding ring, on the leg at the site of varicose veins or at any other site where trauma has occurred. The third type is most common on the elbows and knees and responds quite slowly to the administration of nicotinic acid. It may finally clear by complete desquamation of the thickened layer, revealing new pink epithelium of normal texture underneath. The perineal and genital lesions respond rapidly (in five to eight days) to therapy. Their exact cause is not clear. The remaining types of lesions have already been shown to be due to coexistent deficiencies of other members of the vitamin B complex.

The lesions in the mouth are equally characteristic and diagnostic of the disease. All of the mucous membranes may be involved in an acute inflammatory process which often goes on to ulceration. The tongue, particularly the margins and tip, becomes extremely sore and fiery red, and the papillae, especially the filiform type, tend to marked atrophy so that in the advanced stage they may disappear, leaving the tongue cracked, dry, smooth and glazed. Along the gum margins are collections of necrotic material which contain the fusiform and spirochetal organisms of Vincent's angina. The buccal mucous membranes also may

be swollen, tender and ulcerated. The gastric mucosa shows much the same condition, and frequently the vagina and rectum are affected.

In mild aniacinosis the tongue changes may be of minor order. According to Kruse,[4] the picture includes lingual atrophy, fissures and dental scalloping of the lingual edges. These changes may be reversed by daily supplements of 50 mg. of nicotinic acid for many weeks; the addition of other B factors does not seem to offer further benefits.

The entire subject of oral changes in deficiencies of the B complex is still very confused. To identify a certain change with lack of a specific factor is extremely difficult and often impossible because of response to a variety of pure factors. Generally speaking, however, lingual atrophy almost invariably means B complex deficiency.

Complete absence of gastric secretion is present in well over half of all pellagrins. The stools, of whatever consistency, are nearly always foul. Low levels of plasma protein are usually found. Determinations of nicotinic acid and coenzyme in the blood are difficult but have been made in both treated and untreated patients, with no significant variations apparent. The coenzyme content of blood does not vary significantly even during the most severe stages of the disease, except after therapy with large doses of nicotinic acid. This temporary rise occurs also in normal individuals and is followed under both normal and abnormal conditions by a slow return to normal over a

[4] Kruse, H. D.: Milbank Memorial Fund Quart., 20:262, 1942.

period of days or weeks. The coenzyme content of tissues is probably below normal in pellagrins, but its estimation is not a practical procedure for clinical purposes.

Estimation of nicotinic acid in the blood is being studied, but the methods available are difficult and uncertain, and the variations of this substance in health and disease are not yet completely known. However, the blood level for healthy adult human beings has been variously reported at from 0.15 to 0.5 mg. per 100 cc. of whole blood.

Slightly more promising has been the investigation of the urinary excretion of nicotinic acid. Here, however, the situation is complicated by the multiple pyridine compounds present in the urine, which represent various excretory forms of the vitamin. Chief among these are nicotinic acid, nicotinamide, nicotinuric acid and N'-methylnicotinamide. The compound formerly measured as trigonelline is now known to be the N'-methylnicotinamide, or F_2, which normally represents more than 90 per cent of the total excretion of nicotinic acid derivatives. The remaining 6 or 7 per cent is made up of nicotinic acid and nicotinamide.[5] It is doubtful that nicotinuric acid is excreted under normal conditions, although it does appear after ingestion of nicotinic acid. The total excretion of these derivatives in normal adults has been reported to average 19.8 mg. with an intake of 21 mg. N'-methylnicotinamide produces a fluorescence by which it can be measured quan-

[5] Johnson, B. C.; Hamilton, T. S., and Mitchell, H. H.: J. Biol. Chem., 159:231, 1945.

titatively. In pellagra it is not present in the urine, or is present in only minute amounts, but excretion rises sharply with the administration of nicotinic acid.[6] It is doubtful that this compound possesses anti-blacktongue activity, but it has been reported to improve many of the manifestations of pellagra in humans. Its estimation in urine is the best means thus far developed for a chemical method of diagnosis of deficiency states.

A pigment is known to occur in the urine of pellagrins which was thought originally to be a porphyrin, and its presence appeared to offer a possible diagnostic test for that disease. The pigment now seems more probably to be urorosein or some other indole derivative. Its structure is not known beyond the fact that it is not a porphyrin, and it has been found to occur in many conditions other than pellagra. Its appearance in the urine therefore has no diagnostic importance, at least not until more is known about its chemical nature and behavior.[7] That increased urinary excretion of coproporphyrin actually may occur in pellagra has been demonstrated by numerous investigators, but it has been associated with coexisting liver damage rather than with the pellagra and has been observed almost entirely in alcoholic pellagrins or in others with demonstrable liver impairment.[8]

Kruse[4] has described lingual changes which he believes are among the earliest manifestations of aniacinosis. These lesions are visible grossly but are detectable at an earlier stage through the use of a

6 Huff, J. W., and Perlzweig, W. A.: J. Biol. Chem., 150:395, 1943.
7 Watson, C. J., and Layne, J. A.: Ann. Int. Med., 19:183, 1943.
8 Rimington, C., and Leitner, Z. A.: Lancet, 2:494, 1945.

biomicroscope or slit lamp. The changes consist of early vascular hyperemia followed by hypertrophy of the papillae, particularly of the fungiform type. This imparts to the tongue the stippled or "strawberry" appearance, most common at the tip. General redness and swelling follow, accompanied by marginal indentation and baldness. Fissures, crevices and loss of substance are common especially in the chronic form. Atrophy almost always involves the fungiform before the filiform papillae. Thus lingual atrophy, long recognized as a part of the pellagra picture, may be due to a specific lack of niacin, and in the early stages it may provide us with a badly needed criterion for diagnosis.

It is obvious that pellagra, as it occurs in human cases, is a multiple deficiency. This seems only reasonable because of the close association of the various components of the B complex in their natural occurrence. For this reason, cheilitis, beriberi heart and other lesions are often associated with the manifestations usually accepted as typical pellagra. It now seems clear from the work of many investigators that complete cure of pellagra will not take place through the administration of nicotinic acid alone, particularly if the deficient diet is maintained. For this reason it has been found necessary to supplement the nicotinic acid therapy by addition of riboflavin, thiamine, vitamin B_6 and even some of the unidentified members of the complex, as well as ascorbic acid and vitamin A, before complete cure is effected.

Therapy for pellagra as suggested by Spies and his

associates consists of the daily administration of nicotinic acid or nicotinic acid amide in divided doses totaling 500 mg. daily. If severe nausea and vomiting are present, it may be given parenterally, either subcutaneously or even intravenously, but the quantity should then be reduced to not more than 25 mg. per dose, and a total daily administration of 50 to 100 mg. Ordinarily the medication can be given orally and absorption is satisfactory. The only troublesome reaction is the peripheral vasodilatation, particularly of the face and neck, which occurs usually 15 minutes to 1 hour following the oral dose. This is accompanied by a sensation of intense warmth, tingling and itching in the affected skin. The reaction is transient, disappearing after 15 to 20 minutes, and is of no significance except for the mild discomfort it produces. It tends to be distinctly less prominent when the medication is given with meals. The vasomotor reaction is not caused by nicotinic acid amide, and this compound is therefore to be recommended, since its antipellagric activity is the same as that of nicotinic acid. A total dosage of 500 mg. daily is probably slightly in excess of the amount required to produce prompt improvement in clinical manifestations, but there is no contraindication to using the larger dosages since untoward or toxic results have not been encountered. The dosage for acute deficiencies suggested by the Council on Foods and Nutrition of the American Medical Association is 100 mg. twice daily for a period of weeks. For chronic states the recommendation is 100 mg. twice daily indefinitely.

The lethal dose in rats seems to be about 5 Gm. per Kg., and while a similar figure for man is not available, nevertheless doses of several grams have been given to humans over a single 24 hour period without either immediate or delayed toxic effects except, of course, the vasodilatation already mentioned. Subsidence of symptoms under this therapy is dramatic. The mental picture clears almost overnight—certainly within two or three days. Healing of the skin lesions begins almost immediately and proceeds rapidly, usually by the formation of new, healthy skin under the old scaling areas, with subsequent complete removal of the latter. The mucous membrane lesions heal promptly, and Vincent's organisms disappear from the gum ulcerations within 48 hours. Appetite is improved, and a normal sense of well-being reappears. The peripheral neuritis which is so often present does not respond to this therapy but seems to improve gradually on the addition of thiamine. Cheilitis, when present, and the other oral lesions are further improved by the addition of riboflavin supplements. The specific value of pyridoxine in the clinical complex of pellagra is questionable. The original reports of its value in assisting in the restoration of muscular strength have not been substantiated by further trials. An important part of the treatment of pellagra should always be the supplying of an abundance of protein of high quality to restore depleted protein reserves and to provide an adequate intake of tryptophan, which has been lacking in the pellagra-producing diet. An adequate intake of protein means 100-150 Gm. daily;

this can be administered intravenously in the form of plasma, whole blood or amino-acid digests if food is not tolerated by mouth.

The initial daily dose of niacin of 300 to 500 mg. should be continued for seven to ten days, after which it can usually be reduced to 100 mg. daily or even less, since the skin, mucous membrane and central nervous system lesions usually will have disappeared by that time. Exact information concerning the size and duration of dosage must await quantitative excretion studies to establish speed of saturation of body stores. However, there is no reason why the patient cannot go on a normal adequate diet without added vitamin supplements as soon as the clinical manifestations of the disease have cleared.

Supplementary medication should include thiamine, riboflavin and probably all the other known members of the B complex even though the part that each plays in the pellagra syndrome is not known. These factors may be administered in preparations of whole liver. Vitamin A or carotene, ascorbic acid and vitamins D and E must also be included. A good general diet of high caloric value (2,500-4,000 calories) should be used, with particular attention to its content of meat, eggs, milk and fresh vegetables. The prevention of recurrence of acute exacerbations is, unfortunately, not entirely a medical problem, for economic necessity and eating habits are usually the underlying cause of dietary inadequacy.

Mention should be made of "niacin encephalopathy," a condition which occurs chiefly in pellagrins

and chronic alcoholics. The clouding of consciousness and delirium are similar if not identical to the disturbed mental state of severe endemic pellagra. The effect of niacin on this picture is dramatic and has substantially lowered the mortality.

The use of nicotinic acid to abort attacks of migraine is also worthy of consideration. Administration of 100-200 mg. by mouth during the pre-headache phase of the attack will often prevent the development of the later stages. This effect evidently depends on the vasodilating action of the compound, since niacinamide is ineffective. There is, therefore, no reason to believe that this function is related to the nutritional rôle of niacin.

Many clinical conditions other than pellagra have been treated with nicotinic acid since that vitamin has been available in pure crystalline form. It is justifiable to point out, however, that in none of these instances has this therapy been established on a satisfactory quantitative basis, and the treatment for that reason needs a critical evaluation which only time and the availability of adequate assay methods will eventually provide. Among these various pathologic states may be mentioned peripheral vascular disease, rheumatoid arthritis, high tone deafness, nephrotic edema, atypical psychotic states associated with malnutrition, delirium tremens, glossitis occurring in alcoholism, stomatitis, lupus erythematosus, sprue, toxic manifestations following sulfanilamide administration, nausea and vomiting attending irradiation therapy, chronic ulcerative colitis, multiple sclerosis and por-

phyrinuria of lead intoxication, and all grades of sub-clinical pellagra.

Many other chemical compounds closely related to nicotinic acid have also been used in treatment of blacktongue in dogs and pellagra in humans. Of these, some have shown antipellagric activity and others have proved inert. None of them has shown a higher potency than either nicotinic acid itself or nicotinic acid amide, and none has any apparent advantage over these two compounds. Of particular interest have been the trials with quinolinic acid, N'-methylnicotinamide and various nicotinic acid precursors in food. It is now well established that the activity of niacin may be tied up chemically by esterification and other forms of conjugation so that it becomes metabolically unavailable in nutrition. Hydrolysis restores the activity of these forms.

The ultimate solution of the pellagra problem in this country as well as elsewhere will be difficult, because of its inseparable connection with the economic status of large sections of the population. The fortification of foods throughout these endemic areas is one possibility, but many investigators familiar with the conditions existing in these sections continue to feel that the only true solution will be the gradual adoption, through the help of public health agencies, of a dietary incorporating adequate amounts of all the necessary food factors. It is important to emphasize, however, that no amount of social pressure or even economic aid from without can effectively alter the dietary habits of a population overnight. It will be, at

best, a slow gradual process of reeducation combined with all available economic measures which may help to raise the standard of living of this marginal stratum of society. Methods for temporary amelioration of this situation are discussed in Chapter XIX.

OTHER B COMPLEX FACTORS

PYRIDOXINE

Vitamin B$_6$ is the name applied to that fraction of the vitamin B complex, a deficiency of which produces a characteristic dermatitis in rats. Its existence was first suspected in 1934, as the manifold manifestations of deficiency of the B$_2$ complex were studied in various experimental animals. During the course of these investigations, this factor has been variously known as factor X, factor I, adermin, antiacrodynia vitamin, rat antidermatitis vitamin and, when its chemical structure was finally worked out, as pyridoxine. This last-mentioned name is descriptive of its structure and hence is the most acceptable for a permanent vitamin nomenclature. The American Institute of Nutrition officially accepted the designation in 1940.

Pyridoxine was isolated in pure form in 1938, and definition of its structural formula followed almost immediately. Synthesis was first effected in 1939, following which the pure synthetic material became available for experimental work, enabling investigators to explain many of the inconsistencies which had existed concerning the action of this substance. The structure (Fig. 19) illustrates a second vitamin fraction (nicotinic acid is the other) which has proved to be a pyridine derivative.

The occurrence of pyridoxine in Nature follows the general distribution of the B complex. Table 8 gives its content in several common food sources. Among the animal tissues kidney and muscle are the richest sources, containing 20-30 mg. per 100 Gm. dry weight of tissue. Heart and liver are moderately good and spleen, pancreas, brain and lung poor sources. Cod and salmon are rich in pyridoxine, and wheat germ is about as potent as beef muscle.
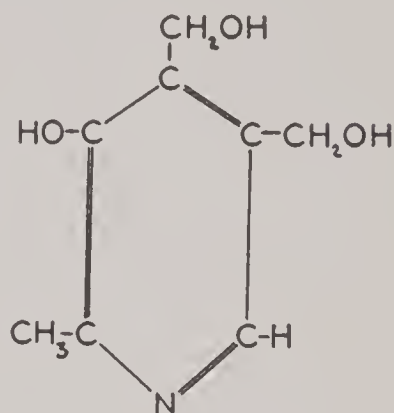
Fig. 19.—Vitamin B₆ or pyridoxine.

Much has been learned in the past five years concerning the biochemical rôle of pyridoxine in metabolism. Lepkovsky and Neilsen[1] found that the urine

TABLE 8.—Pyridoxine Content of Foods*

	Mg. per 100 Gm.
Yeast, brewers'	2.47
Yeast, Fleischmann's	3.95
Yeast extract	1.03
Wheat germ	1.03
Skim milk powder	0.38
Whole milk	1.25
Quaker rolled oats	0.25
Split peas	0.40
Leg of lamb	0.45
Beef liver	0.81
Liver powder (Wilson)	1.45
Nitab (rice-bran concentrate)	5.17

* These figures are taken from unpublished assays provided by Dr. C. A. Elvehjem.

of pyridoxine-deficient rats contains a green pigment, later identified as xanthurenic acid, a product of tryptophan metabolism. Kynurenine is another interme-

[1] Lepkovsky, S., and Neilsen, E.: J. Biol. Chem., 144:135, 1942.

diate in the metabolism of this amino-acid, and the excretion of both substances has been shown to parallel the intake of tryptophan in pyridoxine deficiency. These observations provided the clue to the fact that pyridoxine occupies some fundamental position in the metabolism of tryptophan. Its function appears to be that of a coenzyme in the decarboxylation of this amino-acid. Later studies demonstrated a similar effect in the metabolism of tyrosine, arginine and glutamic acid, and the view now seems justified that this vitamin acts specifically in protein metabolism as a coenzyme for general decarboxylation of amino-acids. In its absence these reactions cannot proceed and the breakdown is diverted into abnormal channels. Mention should be made of the related compounds pyridoxal and pyridoxamine, both of which can function satisfactorily in these reactions. The vitamin and its derivatives apparently must all be phosphorylated in order to serve as coenzymes, and this probably occurs through a preliminary conversion of all forms to pyridoxal, the active form of the vitamin. It is not yet possible to interpret these observations in terms of either clinical or experimental deficiency disease.

Pyridoxine deficiency in rats causes a scaly skin lesion, "rat acrodynia," characterized by hyperkeratosis and acanthosis of the ears, paws and snout and edema of the corium. It is strikingly similar to, if not identical with, that occurring with the lack of certain unsaturated fatty acids, notably linoleic. The exact interrelationship of these two conditions remains obscure,

although it is believed that fat exerts a sparing action on pyridoxine, and certain of the deficiency manifestations can be cleared by supplementing the diet with either factor. The failure of pyridoxine-deficient animals to convert protein into fat emphasizes again the effect already outlined of this vitamin on protein metabolism.

A lack of pyridoxine in dogs and swine produces a microcytic hypochromic anemia which responds only to vitamin therapy. Swine develop, in addition, epileptiform convulsions, an abnormal incoordinated gait and degenerative lesions in the large peripheral nerves, which in later stages progress to involve the dorsal root ganglions.[2]

Reid and his co-workers[3] reported the importance of pyridoxine in the cure of a specific type of poikilocytosis in dairy cattle. Supplements of other members of the B complex had no effect. The function of pyridoxine appears to be solely that of correcting the abnormal shape of the red cells without affecting either hemoglobin or red cell production.

The relation of pyridoxine to human nutrition has been subjected to several critical studies, but thus far no definite function has been assigned to it. It is excreted unchanged in minute amounts in the urine under normal conditions, and after a 50 mg. test dose administered intravenously, amounts recoverable in the urine at one hour vary from 8.4 per cent in adults

[2] Follis, R. H., Jr., and Wintrobe, M. M.: J. Exper. Med., 81:539, 1945.
[3] Reid, J. T.; Huffman, C. F., and Duncan, C. W.: Arch. Path., 39:351, 1945.

under 50 to 21.3 per cent in children between 5 and 15. Both man and dogs excrete relatively large amounts of the vitamin in conjugated form as either a glucuronide or ethereal sulfate. It is probably present in the urine in still other forms, but all can be measured by a chemical method devised by Scudi which appears to be simple enough to serve as a basis for careful quantitative clinical studies.

In the search for a symptom complex in humans which may be attributed to a lack of pyridoxine, it is natural to use animal experiments as guides. In every instance the results have been inconclusive and disappointing. One of the most promising therapeutic trials for a short period was with pyridoxine for the nausea and vomiting of pregnancy. Unfortunately, the studies were poorly controlled, and the condition is one in which psychologic factors are known to be extremely important. However, by using suitable placebo controls Hesseltine[4] has shown that the results with pyridoxine are no better than, and actually not as good as, those with distilled water.

Cantor and Scott[5] reported successful use of pure pyridoxine hydrochloride in doses of 125-200 mg. daily intravenously for granulocytopenia of toxic origin in humans. Response in the white blood cell count appeared as early as the second day of therapy and reached a peak in eight to 10 days. This action appears to result from direct stimulation of the myelocytic elements of the bone marrow. Final evaluation of these

4 Hesseltine, H. C.: Am. J. Obst. & Gynec., 51:82, 1946.
5 Cantor, M. M., and Scott, J. W.: Science, 100:545, 1944.

results must await prolonged extensive clinical trial.

Using the test dose technic, patients with posten-cephalitic Parkinson's disease have been found to excrete only 2.5 per cent of the test dose, lending pos-sible support to the theory that a deficiency of this factor may exist in that disease. Nevertheless the re-sults of therapeutic trials, using doses up to 100 mg. daily for four consecutive weeks have been discourag-ing, and a tentative evaluation at this time would seem to indicate that pyridoxine has little to offer in treat-ment of that disease.

Even less impressive have been the results of thera-peutic trials of pyridoxine in progressive muscular dystrophy, amyotrophic lateral sclerosis, multiple sclerosis and tabes dorsalis, either with or without the simultaneous use of alpha tocopherol. Investigations have been adequate to justify the conclusion that pyridoxine is unrelated to those diseases, both in eti-ology and in treatment, except so far as its administra-tion may improve general nutrition.

The successful treatment of cheilosis with pyridox-ine has been reported and confirmed. The explanation of its efficacy, however, remains obscure, but it is sug-gested either that the condition represents a nonspe-cific deficiency or that the addition of pyridoxine to the diet potentiates or facilitates the utilization of the available riboflavin.

The effect of this vitamin on hemoglobin regenera-tion in the induced anemias of dogs and swine has not been satisfactorily demonstrated in man. A few iso-lated reports have suggested a favorable response in

both microcytic and macrocytic anemias, but most of these studies have been disappointing. It is not known whether pyridoxine bears any relation to poikilocytosis in humans or not. The therapeutic value of this vitamin in pellagra and peripheral neuropathies of all types remains unsettled; despite an occasional encouraging report, it is evident that a clearcut relationship to lesions of the nervous system, similar to those in experimental animals already mentioned, has not been established in humans. The search for evidence of clinical usefulness goes on; students of human nutrition continue to believe that the true function of pyridoxine in clinical medicine will eventually be found.

CHOLINE

Choline has been recognized for many years as a component part of the phospholipid, lecithin, but its significance in nutrition was not appreciated until 1932, when Best and his associates reported that choline was the active portion of the lecithin molecule which prevented the development of fatty liver in depancreatized dogs. A vast amount of research on this problem in the past few years has served to clarify somewhat the physiologic action of this substance. There is some disagreement, however, as to whether choline should be included in the vitamin B complex and, indeed, whether it should be classed as a vitamin since there is experimental evidence of a capacity for limited synthesis in some animals at least, provided the necessary precursor materials are available.

It is now believed that the type of fatty liver occur-

ring in depancreatized animals is characterized by a high content of cholesterol and cholesteryl esters and that choline is not the missing lipotropic (fat-mobilizing) agent. This type probably occurs also in humans with diabetes mellitus. Another common but distinctly different type of fatty liver is produced by a high fat diet, by a low protein diet, by a deficiency of choline or
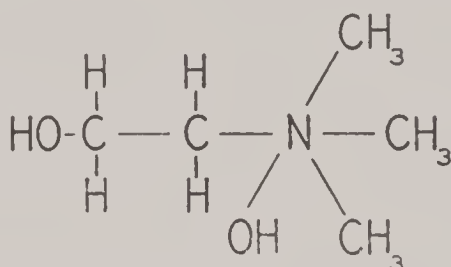
Fig. 20.—Choline.

by a combination of these. The presence of thiamine in the diet is believed to be necessary for these changes to occur, and moderate supplements of choline will either prevent the accumulation or hasten the removal of the fat deposits which in this instance are composed largely of glyceryl esters and are low in cholesterol.[6] In contrast with most other vitamins, the choline requirements of animals are relatively high (0.1 per cent of the diet for rats).

From the biochemical standpoint, the known functions of choline may be stated as follows: (1) A reservoir of labile methyl (CH_3) groups which are available to the body for the synthesis in vivo of such important compounds as creatine, creatinine, epinephrine, trigonelline, sarcosine and the amino-acid, methionine, as well as for certain detoxication reactions.

[6] McHenry, E. W., and Patterson, J. M.: Physiol. Rev., 24:128, 1944.

(2) One of the constituents from which acetyl choline is synthesized. (3) A constituent of the phospholipids, lecitin and sphingomyelin which are thought to function in an important way in the mobilization and

METHIONINE   HOMOCYSTINE

CHOLINE→ METHYL POOL →CREATINE

BETAINE   ETHANOLAMINE
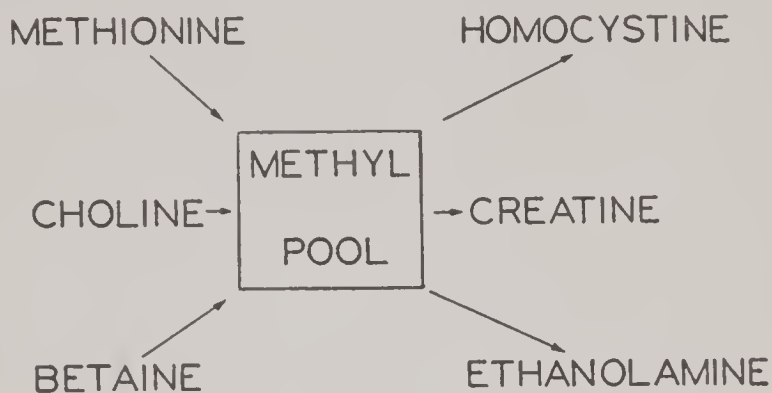
Fig. 21.—Methyl pool.

transport of fat in vivo. The labile methyl pool can be represented schematically, as in Figure 21.

The protective action of choline on liver cells may depend on its contribution to the labile methyl pool or on some other, more fundamental, function which is not understood. Its lipotropic effect probably occurs, at least in part, as a result of the ability of choline to stimulate the formation of phospholipids, which are well known as the transport form for fat. The labile methyl groups do not seem to be important in this regard, but there is evidence that the hydroxyl group is necessary. Certainly there is sound evidence that an abundant dietary supply of choline accelerates the turnover of liver fat in the form of phospholipid.

Choline deficiency in experimental animals produces a series of characteristic changes, the most important of which are an accumulation of fat in the liver, an

extensive acute hemorrhagic nephritis and marked regression of the thymus. The pathogenesis of these lesions in terms of biochemical reactions is still unknown.

The prevention of the fatty liver changes and the ensuing cirrhosis in experimental animals by means of choline has led to a therapeutic trial of this substance in human cases of cirrhosis. Its administration in doses of 1 to 3 Gm. daily by mouth has produced definite and striking improvement in certain individuals, particularly in those with early cases in whom the pathologic process is chiefly or partially fatty degeneration. Figure 23 (p. 146) shows a section from such a case. Thus choline appears to manifest the "lipotropic" action in humans that is well known experimentally, but it has not been shown to possess any special liver-regenerating power, nor does it cause any apparent dissolution of connective tissue which has already formed. One of the most encouraging reports on the use of choline in human cirrhosis is that of Russakoff and Blumberg.[7] Their results in a small series of cases do not provide statistically significant data, but suggest that choline has a beneficial effect in cases with predominantly fatty liver changes. It is generally agreed that late cirrhosis does not respond. In infectious hepatitis and toxic liver necrosis the results with choline have been most disappointing. Beams[8] reported almost the same type of result.

The treatment of liver cirrhosis has undergone im-

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[7] Russakoff, A. H., and Blumberg, H.: Ann. Int. Med., 21:848, 1944.
[8] Beams, A. J.: J. A. M. A., 130:190, 1946.

portant changes in recent years as a result of excellent experimental work indicating that nutritional deficiency is one, and possibly the most important, etiologic factor in the disease. The older classic high carbohydrate diet has been replaced by a high protein diet (over 100 Gm. daily) augmented by brewers' yeast and other vitamin concentrates. Carbohydrate is maintained at a moderately high level and fat reduced to a minimum. The results have been much more encouraging than those with the older regimen. It is probable that the efficacy of this new plan of management may be attributed, in part, to the large amount of choline and other lipotropic factors which it provides. A more complete discussion of this problem is included in the section on Proteins.

Choline is being tried more or less empirically in a great variety of clinical conditions, among them hemolytic anemia, various forms of neuropathy and some skin disorders. The reports, however, are fragmentary and the results equivocal, so that a detailed discussion does not seem justified at this time.

PANTOTHENIC ACID

Pantothenic acid, formerly known as the chick antidermatitis factor, was separated from the filtrate factor (the remaining mixture of components), and in 1940 it was crystallized, its structure determined and synthesis performed. In experimental animals a deficiency of this factor produces pathologic changes in the central nervous system, and apparently has

important effects on the endocrine glands. These have been investigated in several animal species.

Great interest has been aroused by the demonstration that pantothenic acid is essential for the integ-

$$\text{HO-}\underset{\overset{|}{H}}{\overset{\overset{H}{|}}{C}} - \underset{\overset{|}{CH_3}}{\overset{\overset{CH_3}{|}}{C}} - \underset{\overset{|}{H}}{\overset{\overset{OH}{|}}{C}} - \overset{\overset{O}{|}}{C} - \underset{}{\overset{\overset{H}{|}}{N}} - \underset{\overset{|}{H}}{\overset{\overset{H}{|}}{C}} - \underset{\overset{|}{H}}{\overset{\overset{H}{|}}{C}} - C\overset{\nearrow O}{\searrow_{OH}}$$
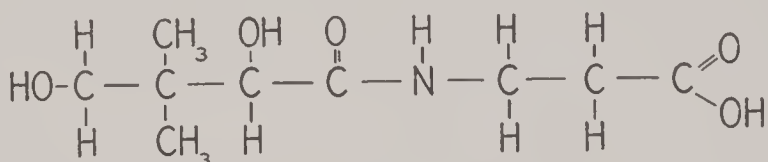
Fig. 22.—Pantothenic acid.

rity of the adrenal gland. In experimental animals made deficient in this nutrient, extensive hemorrhagic necrosis in the adrenal cortex regularly appears. This lesion progresses to the death of the animal, but it has been possible to maintain life in both rats and dogs under these conditions by administration of adrenal cortical extract. Figure 24 shows the characteristic destructive lesion. Thus the structural changes are accompanied by physiologic manifestations of adrenal insufficiency. Degenerative changes in the thyroid and testes have also been described in these animals.

The abundant confirmation of these experimental findings has served to make clinical investigators alert to the possibility of endocrine changes secondary to dietary deficiency disease. Although suggestive cases have been studied by a number of observers, there have not yet been published any clearcut instances of this functional interrelationship in humans.

There is no doubt that pantothenic acid under certain experimental conditions may act as an "anti-gray hair factor." Black rats maintained on a pantothenic acid-deficient diet develop extensive graying of the

fur which roughly parallels in intensity the adrenal changes just described. It seems probable that there are other substances which affect the graying of hair. For example, a simultaneous lack of pyridoxine in the diet seems to produce a resistance to graying induced by pantothenic acid deficiency, while para-aminobenzoic acid has been shown to be an anti-gray hair factor under the proper rigid experimental conditions. Attempts to obtain the same results in humans have been uniformly disappointing. A few promising isolated reports have appeared, but there is now overwhelming evidence that in humans the graying of hair is completely unrelated to the intake of pantothenic acid and that the use of this vitamin in large doses over long periods will not restore hair color.

Further correlation of the pantothenate deficiency lesions of the adrenal cortex with the graying of hair in rats was provided by Ralli and Graef,[9] who showed that adrenalectomy will restore hair color of deficient animals, increase the growth rate of hair and accelerate the rate of recovery in gray-haired rats when pantothenic acid is returned to the diet. They also demonstrated that desoxycorticosterone and adrenal cortical extracts will largely prevent the effects of adrenalectomy in these animals.[10] These results are perhaps a little surprising, for there is good reason to believe, on chemical grounds, that the adrenal medulla is involved in melanin metabolism. It is impossible even to guess what implications these findings may have regarding the

9 Ralli, E. P., and Graef, I.: Endocrinology, 32:1, 1943.
10 Ralli, E. P., and Graef, I.: Endocrinology, 37:252, 1945.
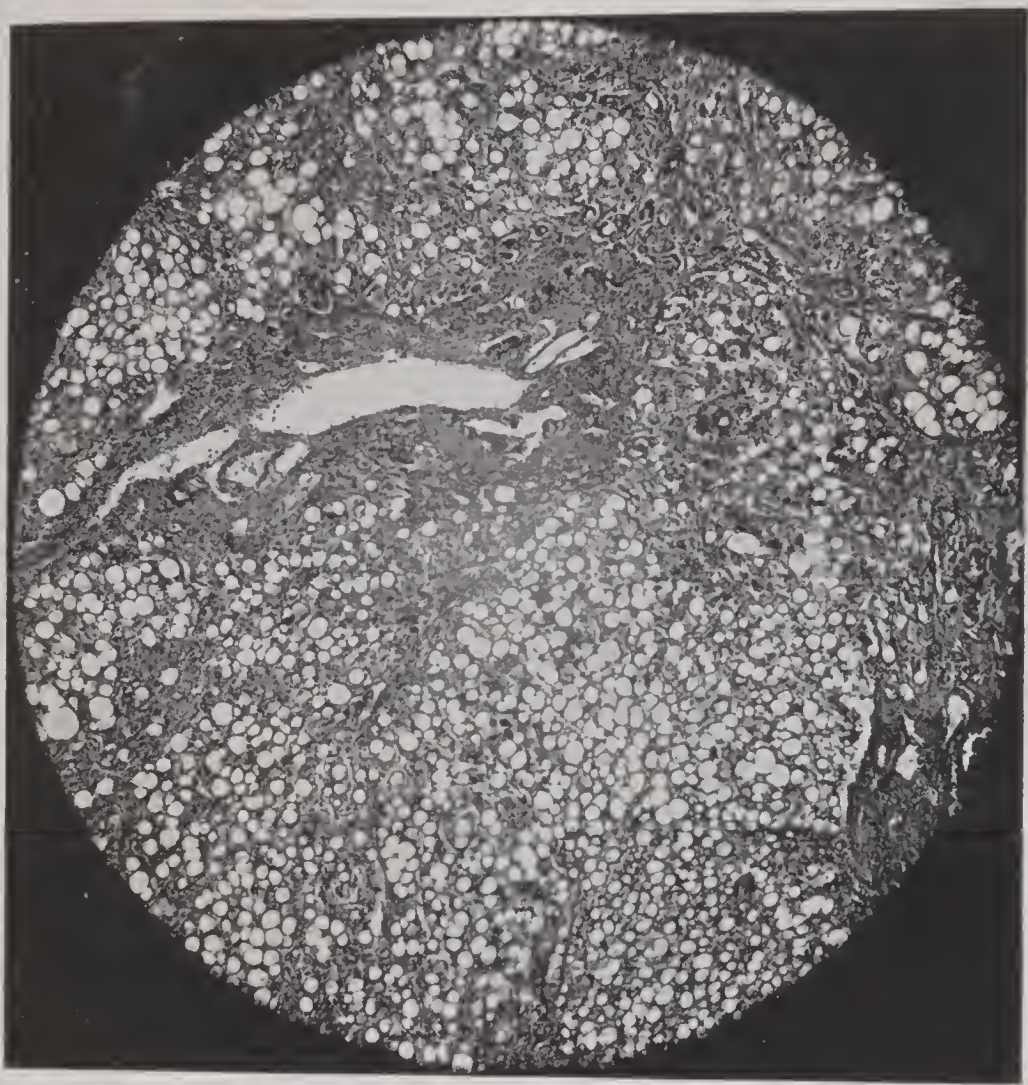
Fig. 23.—Section of liver with fatty degeneration.

Fig. 24.—Characteristic destructive lesion in adrenal gland of a rat with pantothenic acid deficiency.

Fig. 25.—Longitudinal section through spinal cord of chick on diet deficient only in pantothenic acid. Nerve degeneration stains black. (Courtesy of Dr. Paul Phillips, Dept. of Biochemistry, Univ. of Wisconsin.)

problems of growth and of the graying of human hair.

The neurologic consequences of pantothenic acid deficiency have been most successfully demonstrated in chicks and pigs. Spinal cord degeneration occurs in both species (Fig. 25), accompanied by extreme motor impairment. In humans, pantothenic acid supplements have been found to improve the manifestations, both subjective and objective, of peripheral neuritis on a nutritional basis, after thiamine, riboflavin, niacin and pyridoxine had failed to do so. It has also produced rapid and striking amelioration of symptoms in alcoholic psychosis with hallucinations after other pure vitamin B components had failed. Urinary excretion of pantothenate during these deficiency states has been found low, with a prompt rise to normal as soon as supplements were administered, and somewhat preceding clinical improvement. Nevertheless these results are suggestive only and do no more than indicate the direction future observations should take. It must be emphasized that the true functions of pantothenic acid in humans will probably remain unknown until human deficiency of that single factor is produced experimentally.

A few quantitative studies of pantothenic acid in humans have been reported. They establish the presence of this substance in the blood and urine of normal healthy adults in amounts which fluctuate according to the dietary intake. In the blood, the concentration in normal fasting adults varies from 19 to 23 μg. per 100 cc., and about 44 per cent of this is in the plasma. A lowering of from 20 to 30 per cent of these

fasting values occurs after the administration of glucose by mouth, which has made it seem likely that pantothenate is in some manner involved in carbohydrate metabolism. The blood concentrations of all other animal species studied have been much higher than those recorded for humans. The average daily urinary excretion lies in the region of 3.5 mg., with a range of 1 to 7.5 mg., and all patients with general B complex deficiency consistently excrete less than 1 mg. per 24 hours. After a 100 mg. test dose by mouth, 8.8-23.4 mg. above the basal excretion occurs in normal humans, and after a similar dose intravenously, the urinary loss is 22-41 mg. over the basal level.[11,12] It is known that pantothenic acid can be converted into a ring form (lactone) which is inactive in metabolism. The fate of test doses of pantothenate given either orally or intravenously is unknown, since only a relatively small fraction appears in the urine as active pantothenic acid.

Pantothenic acid is synthesized by many bacteria, including many of the normal inhabitants of the gastro-intestinal tracts of man and various experimental animals. When this occurs in the rumen, absorption lower in the intestine of the resulting pantothenate prevents a deficiency state from arising, even though the diet contains none of that factor. In nonruminants, the site of the bacterial synthesis is important, since absorption from the colon is probably rather slight. Despite this, biosynthesis of pantothenic

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11 Gordon, E. S.: in Evans, E. A., Jr.: *The Biological Action of the Vitamins: A Symposium* (Chicago: University of Chicago Press, 1942).

12 Sarett, H. P.: J. Biol. Chem., 159:321, 1945.

TABLE 9.—DISTRIBUTION OF PANTOTHENIC ACID IN FOODS IN
MICROGRAMS PER GRAM

SOURCE	DRIED	UNDRIED
Dried brewers' yeast	200	
Liver	180	40
Egg yolk	125	63
Eggs	108	27
Broccoli	87	14
Cane molasses	70	
Peanut meal		53
Buttermilk, churned	46	4.6
Sweet potatoes	38	11
Lean beef	38	10
Beef liver	240	66
Pork liver	196	55
Beef heart	122	22
Pork loin	68	19
Leg of lamb	50	13
Beef, round	38	
Skim milk	36	3.6
Squash	35	3
Canned salmon	28	7
Irish potatoes	28	6.5
Wheat bran		24
Canned pumpkin	23	4
Whole milk	22	2.8
Rice bran		22
Split peas		21
Tomatoes	20	1
Soy bean meal		14
Carrots	13	2
Rolled oats		11
Wheat		11
Barley		10
Spinach	10	1.2
Onion	9	1.2
Yellow corn		8
English walnuts		8
Oranges	7	0.7
Polished rice		4
Banana	4	0.7
Canned green beans	1.1	
Asparagus	0.9	
Canned green peas	0.7	
Prunes		0.6
Raisins		0.6
Beets	0.4	
Apples	0.3	
Almonds		0.3

acid probably affects significantly the daily require-
ment in humans as well as in experimental animals.
The magnitude of this daily requirement is completely
unknown.

Pantothenic acid originally derived its name from
its almost universal natural occurrence, and the fre-
quency of occurrence of spontaneous pantothenate de-
ficiency in humans is therefore a matter of consider-
able interest. That it may be a part of total B complex
deficiency seems perfectly clear, but the intricate inter-
relationships of the various pure factors, about which
information is only beginning to accumulate, make it
probable that the presence of certain other nutrients
eventually will be proved necessary for the lack of
pantothenate to manifest itself. Experimental work
may soon lead to a definition of the necessary experi-
mental conditions.

The pantothenate content of various foods is given
in Table 9.

BIOTIN

Biotin, formerly known as vitamin H or the "anti
egg-white injury factor," is now known to be a dietary
essential for many species of animals including man,
and a growth requisite for many bacteria and yeasts,
for which it has long been recognized as "coenzyme
R." Its chemical structure is shown in Figure 26.
Synthesis was announced by du Vigneaud[13] in 1942. Its
molecular weight is 244.

Biotin combines chemically with a substance known

13 Du Vigneaud, V.: Science, 96:455, 1942.

as avidin present in large amounts in uncooked egg white. This unusually stable combination, released only by relatively strong hydrolysis, is thought to take place through the urea group of the biotin, one molecule of the latter combining with one of avidin. This antibiotin substance is known to be a protein, prepared recently in crystalline form. It has a molecular weight of about 70,000, and the pure material has 15,000
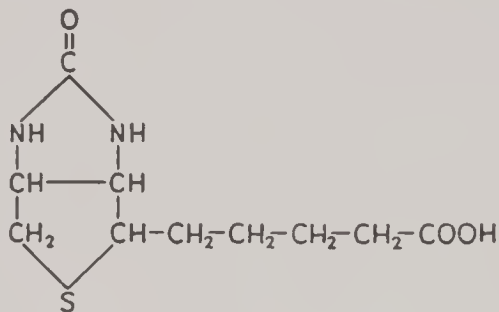
Fig. 26.—Biotin.

times the antibiotin activity of the original egg white. It may be present also in some animal and plant tissues. Its attachment to biotin in the intestinal tract of animals carries the biotin through without absorption, thereby producing tissue depletion, the external manifestations of which have been recognized as "egg white injury." Avidin is not effective when administered by injection; in fact, hydrolysis in the tissues appears to release a small amount of attached biotin which actually helps to relieve preexisting depletion.

The exact biologic rôle of biotin is only beginning to be explored. It acts as a powerful stimulant of growth, respiration and fermentation for certain micro-organisms. It may serve a similar function in animals, mediated in all probability through various

respiratory enzyme systems. It has been shown to cause the deposition of large amounts of fat in the livers of animals receiving otherwise adequate diets. In addition, recent evidence indicates that biotin increases the incidence of certain experimental tumors in animals on protective diets. Supplementation with biotin has also abolished the "protection" of certain diets in these animals, resulting in augmentation of tumor growth. These observations led to the trial of induced biotin deficiency in human cancer patients in the hope of selectively inhibiting the growth of tumor cells, which seem to have an unusually high biotin requirement. The clinical experiments were suggestively hopeful in a few cases, but after considerable trial this approach to the cancer problem must be considered no more successful than all those that have preceded it. The biochemical rôle of biotin in tumor metabolism still needs clarification.

Little is known of human needs for biotin, but on the basis of animal studies the daily requirement must be exceedingly small. The compound is found in almost all plant and animal tissues and is concentrated in young, embryonic or growing organisms. Assays have revealed especially large amounts in yeast and liver and moderate amounts in many animal tissues and a wide variety of vegetables. Its wide distribution in foods and the extraordinarily minute amounts needed in metabolism make the natural occurrence of abiotinosis from dietary inadequacy seem rather doubtful. Certainly the consumption by human beings of enough uncooked egg white over a sufficiently long period to

produce clinical avitaminosis is highly unlikely. Nevertheless experimental biotin deficiency in humans had been produced by the use of a diet with low biotin content supplemented by 200 Gm. of dried egg white daily. All other essential vitamins were supplied in pure form to eliminate the possibility of other complicating deficiencies.

Under these conditions the basal urinary excretion of biotin of 29 to 62 µg. per 24 hours fell during the period of depletion to 3.5 to 7.3 µg. daily, and rose again to normal immediately after the parenteral administration of biotin concentrates. A fine, scaly dermatitis developed in three to four weeks, followed at about seven weeks by the appearance of a maculosquamous lesion accompanied by a peculiar grayish pallor which was out of proportion to the observed reduction in circulating hemoglobin. Other manifestations of the deficiency state consisted of atrophy of the lingual papillae with pallor of the entire tongue and the appearance of a mental state characterized by intense depression with hallucinations changing at times to panic. Appetite failed rapidly so that the total intake of food became much reduced. Signs of coronary ischemia developed, as evidenced by electrocardiographic changes indistinguishable from those usually associated with thiamine deficiency. The bilirubin and cholesterol levels of the blood were both increased. Marked improvement occurred within three or four days after injection of 30 to 75 µg. of biotin daily.[14]

[14] Sydenstricker, V. P.; Singal, S. A.; Briggs, A. P.; de Vaughn, N. M., and Isbell, H.: Science, 95:176, 1942.

Oppel[15] extended these observations in humans. On unrestricted diets, normal subjects excreted from 14 to 111 μg. of biotin daily, and a good correlation between excretion and dietary intake was noted. Seriously ill patients continued to excrete significant amounts of biotin even when their food intake was extremely low. The biotin content of the feces regularly exceeded the content of the diet, and the combined urinary and fecal excretion of biotin was three to six times greater than the dietary intake. Intestinal biosynthesis is therefore an important source of this essential factor in both animal and human nutrition.

That biotin may have some important function in reproduction and lactation is indicated by the fact that both pigs and rats given large amounts of egg white show evidence of fetal resorption, or produce litters either paralyzed at birth or stillborn. Addition of biotin to the diet partially corrected these abnormalities.

Although the exact rôle of biotin biochemically as well as clinically has not been defined, there appears to be a close correlation with rapidly metabolizing tissues, such as fetal and neoplastic. A great deal of further investigation is needed to extend our knowledge of biotin.

INOSITOL

Attention was directed to inositol as a possible dietary essential by Woolley[16] in 1940 in connection with an alopecia in mice fed synthetic diets lacking this

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15 Oppel, T. W.: Am. J. M. Sc., 204:856, 1943.
16 Woolley, D. W.: Science, 92:384, 1940; J. Biol. Chem., 139:29, 1941.

factor. The compound itself was known, but its nutritional significance is still under extensive investigation. The chemical structure is shown in Figure 27.

Inositol is widely distributed in living tissues and is therefore abundant in all well balanced diets. It is also produced in significant amounts in intestinal biosynthesis so that a true deficiency seems improbable. Its biochemical function, which has received perhaps the greatest attention, is its lipotropic effect in the mobilizing of liver fat
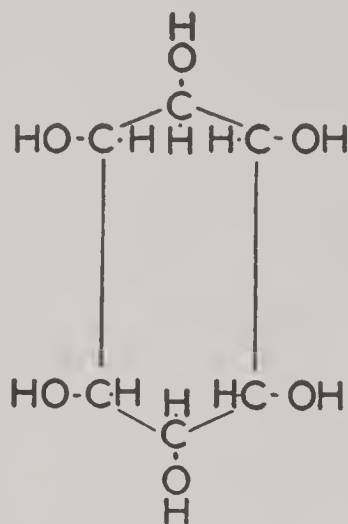
Fig. 27.—Inositol.

under certain conditions, as in the diabetic animal in which the fat consists largely of cholesterol esters. This action was first described by Gavin and McHenry[17] in 1941. Choline is effective in another type of fatty liver which commonly occurs with alcoholism and other types of dietary deficiency, and its action does not replace that of inositol. Although there is some disagreement among investigators over much of this work, it is generally conceded that choline and inositol are at least complementary in their actions as lipotropic factors.

Woolley[18] described a phosphatide-like compound found in soybean oil, called liposterol. It contains 16 per cent inositol, galactose, tartaric acid and both saturated and unsaturated fatty acids. This may perhaps be the substance involved in the reported effect of a

[17] Gavin, G., and McHenry, E. W.: J. Biol. Chem., 139:485, 1941.
[18] Woolley, D. W.: J. Biol. Chem., 147:581, 1943.

combination of inositol and vitamin E in muscular dystrophy. The results of extended trial of this therapy in dystrophy have been disappointing; they are more fully discussed in the chapter on Vitamin E.

Inositol occurs in both combined and free form in most animal tissues. In the heart it is present to the extent of 1.6 Gm. per 100 Gm. dry weight of tissue. Combined inositol makes up about half of the total in most tissues; it is probably not available for use when included in the diet. This may be true of the inositol in many types of animal and plant foods.

It is obvious that the place of inositol in the general metabolic scheme is little known. Nevertheless, the available leads should direct further studies in both experimental and clinical fields until the function of this material is clearly defined.

PARA-AMINOBENZOIC ACID

Two chemical compounds have been found which possess anti-gray hair potency under certain experimental conditions in animals. Pantothenic acid, mentioned previously, effectively restores the hair color in animals previously made gray by a diet lacking in the "filtrate factor." It is noteworthy, however, that the dose of pantothenate needed is relatively larger than the usually accepted requirement of the animal. The other compound is para-aminobenzoic acid (PAB), also shown to possess this activity in rats and mice. This substance, generally speaking, is less effective than pantothenic acid in the prevention of gray hair, but regardless of their effects in animals it may be

flatly stated that neither factor has any effect on the graying of hair in humans.

Para-aminobenzoic acid is not a new compound. Its membership in the B group of vitamins was suggested in 1942 by the observation that it had a sulfonamide-inhibiting effect on certain micro-organisms and seemed to be a growth requirement under experimental conditions. It was next found to promote growth in chicks and to prevent the appearance of gray hair in rats and finally even in man. There has developed, however, some doubt whether it should be included in the B complex. This skepticism has been increased since the discovery that para-aminobenzoic acid is a constituent of the folic acid molecule, and the question remains to be settled.

The only application of interest to clinical medicine is the use of PAB in the treatment of some rickettsial diseases—typhus, scrub typhus and Rocky Mountain spotted fever. In experimental infections in animals its effect has been clearly demonstrated, and the clinical application has been gratifying, especially in view of the fact that there is no other known chemotherapeutic agent available for these diseases. Yeomans and his associates[19] reported a series treated with PAB in which the disease was much milder and complications strikingly less than in a control group. The dosage was 4-8 Gm. initially, followed by 2 Gm. every two hours. The drug was administered by mouth when possible, usually with sodium bicarbonate to neutralize the acid,

[19] Yeomans, A.; Snyder, J. C.; Murray, E. S.; Zarafonetis, C. J. D., and Ecke, R. S.: J. A. M. A., 126:349, 1944.

but in unconscious patients it was given parenterally. These results justify a hope that a chemotherapeutic defense against rickettsial infections may evolve from these modest beginnings.

FOLIC ACID

The synthesis of folic acid, first reported in August, 1945,[20] represents the culmination of a series of converging lines of investigation begun 10 years before. In 1935 Langston, Day and Shukers[21] described a nutritional factor found in yeast and liver concentrates which would prevent or cure anemia and nutritional cytopenia in monkeys. They named this factor vitamin M. Three years later Stokstad and Manning[22] identified a factor necessary for growth in chicks which they called factor U. Almquist confirmed these observations, and a year later Hogan and Parrott[23] reported the occurrence of a macrocytic anemia in chicks deficient in this factor, which they labeled vitamin B_c. From bacteriologic studies Snell and Peterson[24] in 1940 announced a growth factor necessary for culture of Lactobacillus casei. This substance, first called the "norite eluate factor," was soon named simply the L. casei factor. In the same year Mitchell, Snell and Williams[25]

20 Angier, R. B., *et al.*: Science, 102:227, 1945.

21 Langston, W. C.; Day, P. L., and Shukers, C. F.: J. Nutrition, 9:637, 1935.

22 Stokstad, E. L. R., and Manning, P. D. V.: J. Biol. Chem., 125:687, 1938.

23 Hogan, A. G., and Parrott, E. M.: J. Biol. Chem., 128:(proc.)48, 1939.

24 Snell, E. E., and Peterson, W. H.: J. Bact. 39:273, 1940.

25 Mitchell, H. K.; Snell, E. E., and Williams, R. J.: J. Am. Chem. Soc., 63:2284, 1941.

discovered a similar factor necessary for the growth of Streptococcus lactis R which they named "folic acid" because of its abundance in green leafy plants. A possible relation between the bacterial factor and the factor required by the chick was first indicated when Hutchings and his associates[26] found that a preparation of the L. casei factor was very active in the promotion of the growth of chicks on a synthetic diet. Later Mills and his associates[27] showed this factor to be active in the prevention of anemia in chicks. Black and his co-workers[28] found that rats fed sulfaguanidine showed reduced growth which could be counteracted by the administration of liver extract, and they suggested that the active material was probably related to the L. casei factor.

Thus, over a period of five years five independent groups of investigators described new nutritional factors identified by a variety of biologic tests. In the following five years these paths of research gradually merged, leading to the final isolation and synthesis, by the group at the Lederle Laboratories, of the compound now known as folic acid. This substance possesses biologic and chemical properties which relate it to all of the various aforementioned factors which, though similar, are not identical. The chemical structure of folic acid and the details of its synthesis were first re-

[26] Hutchings, B. L.; Bohonos, N.; Hegsted, D. M.; Elvehjem, C. A., and Peterson, W. H.: J. Biol. Chem., 140:681, 1941.

[27] Mills, R. C.; Briggs, G. M.; Elvehjem, C. A., and Hart, E. B.: Proc. Soc. Exper. Biol. & Med., 49:186, 1942.

[28] Black, S.; Overman, R. S.; Elvehjem, C. A., and Link, K. P.: J. Nutrition, 23:589, 1942.

ported in May, 1946.[29] The structural formula is shown in Figure 28.

There is good reason to believe that the differences observed in the requirements of various animal and bacterial species which have resulted in diagreements among investigators using concentrates of this factor can now be explained by minor variations in the chem-
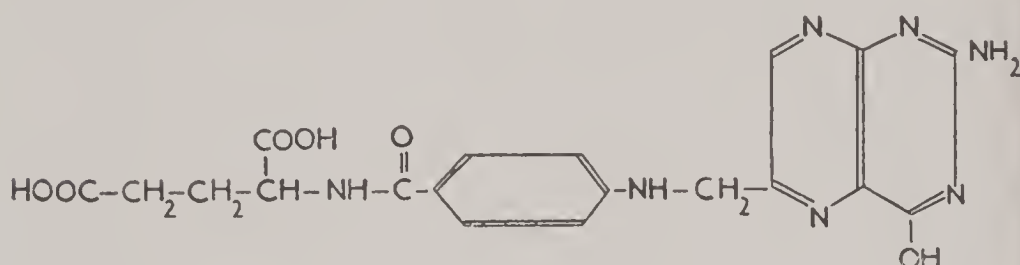
Fig. 28.—Folic acid.

ical structure of the molecule. Some, at least, are concerned with the number of glutamic acid units included in the molecule, and the compound shown in Figure 28 may not be utilized equally well by all test organisms. This circumstance may also explain the complicated relationship of folic acid and the maturation factor in pernicious anemia in humans.

Folic acid occurs almost universally in Nature, being distributed in a wide variety of plant and animal tissues. Its unavailability to different organisms for metabolic purposes suggests that it is probably present to varying extents in both bound and free forms. It is most abundant in green leafy plants and in liver. Milk contains a significant amount of bound folic acid which is not available to micro-organisms but can be used by most animals. Hydrolysis is apparently necessary to

[29] Angier, R. B., *et al.*: Science, 103:667, 1946.

release it. Biosynthesis by intestinal organisms is an important source of folic acid for animals, probably including man. It is interesting that the deficiency syndromes thus far identified involve abnormal metabolism of folic acid rather than an actual dietary deficiency.

Clinical trial of this new substance began immediately after its synthesis, and its value in macrocytic anemia is well established. Spies and his associates,[30] Moore and his co-workers[31] and Darby and Jones[32] have demonstrated the efficacy of synthetic folic acid in the treatment of sprue, nutritional macrocytic anemia, addisonian pernicious anemia and the macrocytic anemia of pregnancy. Folic acid has been administered orally, subcutaneously, intramuscularly and even intravenously, with blood responses in each instance. One of the surprising details of these clinical studies has been the response obtained regularly on oral administration, even in patients with sprue, in whom intestinal absorption is known to be impaired. In macrocytic anemia associated with cirrhosis of the liver and carcinoma of the stomach responses have also been obtained, but in leukemia, aplastic anemia and iron deficiency anemia folic acid is ineffective. Thus it appears that macrocytosis is a prerequisite for successful treatment with folic acid; in all other types of anemia the response to

[30] Vilter, C. F.; Spies, T. D., and Koch, M. B.: South. M. J., 38:781, 1945; Spies, T. D.; Vilter, C. F.; Koch, M. B., and Caldwell, M. H.: South. M. J., 38:707, 1945.

[31] Moore, C. V.; Bierbaum, O. S.; Welch, A. D., and Wright, L. D.: J. Lab. & Clin. Med., 30:1056, 1945.

[32] Darby, F. S., and Jones, E.: Proc. Soc. Exper. Biol. & Med., 60:259, 1945.

RESPONSE OF PERNICIOUS ANEMIA
TO FOLIC ACID

o—HEMOGLOBIN
x—RED CELLS
•—RETICULOCYTES

Fig. 29.

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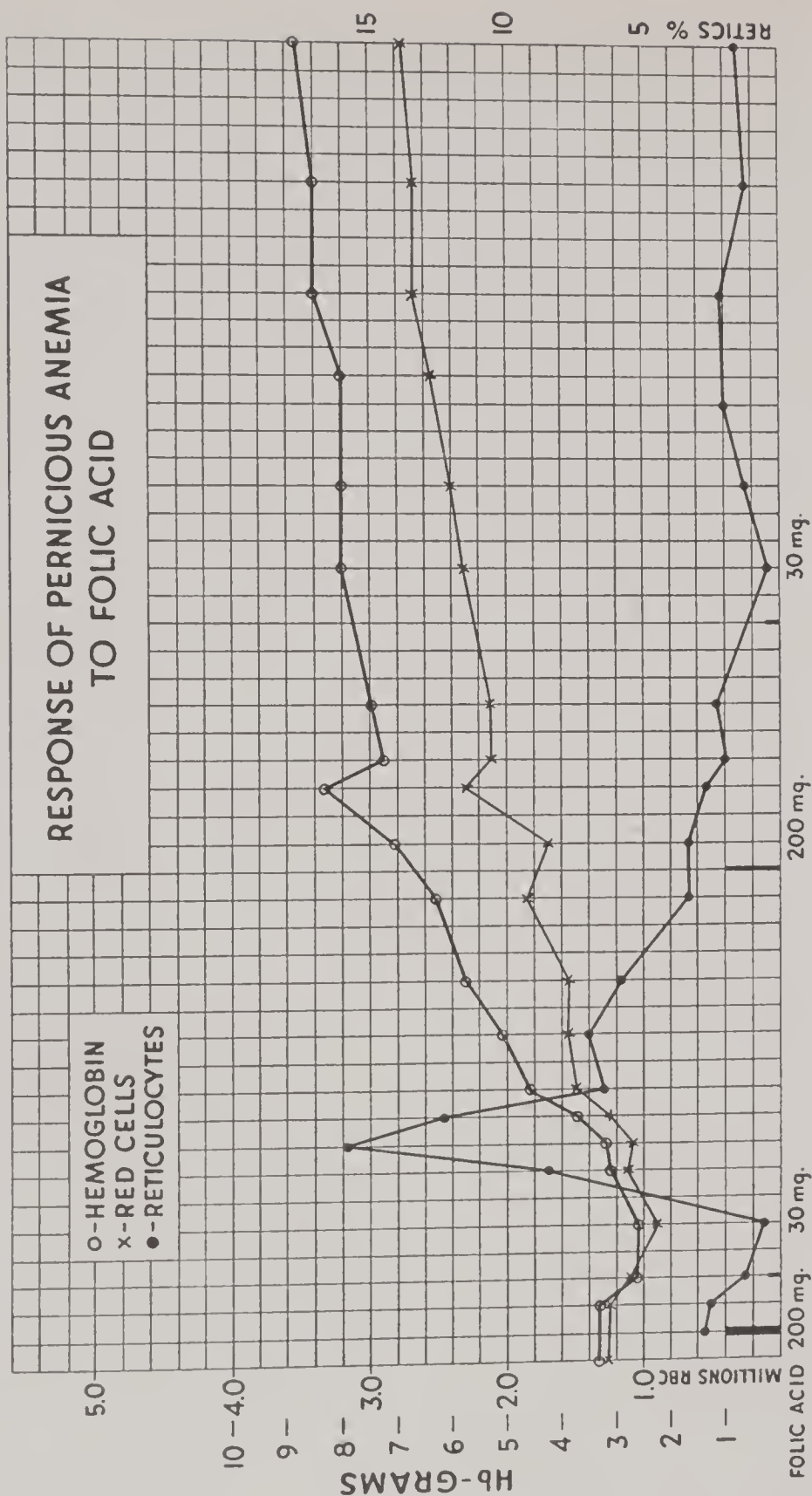
this new material is identical with, and no better than, that to liver extract.

The striking similarity of response of macrocytic anemia to folic acid and liver extract led to the belief that the former is either identical with, or related to, the maturation factor known to be stored in the liver. Castle and his associates[33] have demonstrated that folic acid is not the extrinsic factor, and this opinion was corroborated by Moore. That both the intrinsic factor and the maturation factor contain folic acid remains, however, a good probability, and a considerable body of evidence is available to support this view.

The demonstrated effect of folic acid on the maturation of blood elements and its apparent importance in white blood cell production in both monkeys and man has stimulated considerable interest in its possible rôle in leukemia. Bethell and Swendseid[34] determined the folic acid content of leukocytes in both normal and leukemic subjects. In the normal subjects the values varied from 40 to 180 µg. per cc. of packed cells, with an average of 80 µg. In the leukemic subjects the values varied from 70 to 160 µg., average 108 µg., in lymphatic and from 75 to 220 µg., average of 146 µg., in myelogenous leukemia. The values were depressed toward normal by x-ray treatment. In all cases the folic acid content of leukocytes was correlated directly with the immaturity of cells, the blast cells containing significantly larger quantities. In seven cases of acute

[33] Castle, W. B., *et al.*: Science, 100:81, 1944.
[34] Bethell, F. H., and Swendseid, M. E.: Proc. Am. Soc. Clin. Investigation (1946), p. 18.

myeloblastic leukemia the values were 250 to 800 µg., average 460 µg. It is not possible to interpret these findings at present.

The history of the group of compounds known as the pterins is an important part of the story of the development of folic acid. In 1889 Hopkins[35] first called attention to a pigment from the wings of certain species of butterflies which, because of its chemical properties, he believed to be closely related to uric acid. This compound is now known as xanthopterin, much of the chemistry of which was worked out by Wieland and Schopf.[36] Koschara[37] demonstrated this substance in human urine, and investigation of its rôle in mammalian physiology was begun. Because of its close chemical similarity to the flavins it seemed possible that it might be a constituent of certain oxidative enzyme systems. Meanwhile Tschesche and Wolf[38] showed that injection of xanthopterin cured an anemia in rats fed goat's milk, and Jacobson[39] demonstrated the presence of a yellow pterin in the argen-
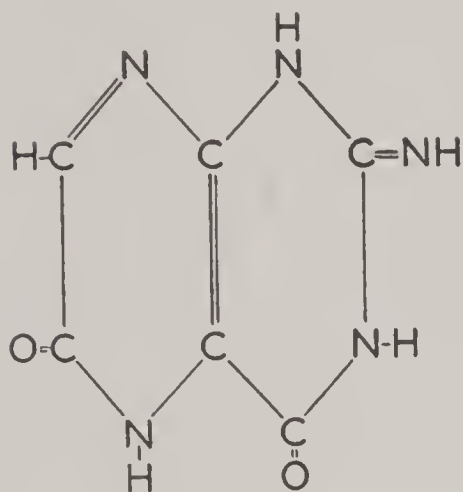
Fig. 30.—Xanthopterin.

35 Hopkins, F. G.: Proc. Chem. Soc., 5:117, 1889.
36 Wieland, H., and Schopf, C.: Ber. deutsche chem. Gesellsch., 58:2178, 1925.
37 Koschara, W.: Ztschr. f. physiol. Chem., 240:127, 1936.
38 Tschesche, R., and Wolf, H. J.: Ztschr. f. physiol. Chem., 248:34, 1937.
39 Jacobson, W.: J. Path. & Bact., 49:1, 1939.

taffin cells of the intestinal epithelium. The chemical structure of xanthopterin is shown in Figure 30.

That xanthopterin is a constituent of the folic acid molecule is obvious on comparison of their respective structures. The distribution of xanthopterin in mammalian tissues corresponds closely with that of the argentaffin cells of the intestinal tract, which are believed also to be the site of formation of the intrinsic factor, important in hemopoiesis. Liver extracts potent against pernicious anemia also contain significant amounts of xanthopterin; thus circumstantial evidence is provided that a pterin molecule is a constituent of the maturation factor. In 1944 folic acid was shown to contain xanthopterin,[40] and folic acid synthesis was based on that fact. The final piece of evidence linking all of these separate lines of investigation was a suggestive therapeutic effect of xanthopterin in pernicious anemia.[41] Of interest also is the report of Frommeyer and his associates[42] of the effectiveness of 5-methyl uracil in inducing a reticulocyte response.

In the assay of all natural sources of folic acid and xanthopterin preliminary hydrolysis is of the greatest importance because both compounds are present in combined form in many foods and tissues. Failure to appreciate this fact has led to erroneous estimates of folic acid content of various crude materials, such as antipernicious anemia liver extract. The observations

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[40] Totter, J. R.; Mims, V., and Day, P. L.: Science, 100:223, 1944.
[41] Heinle, R. W.; Welch, A. D., and Nelson, E. M.: Proc. Am. Soc. Clin. Investigation, (1946), p. 27.
[42] Frommeyer, W. B.; Spies, T. D.; Vilter, C. F., and English, A.: J. Lab. & Clin. Med., 31:643, 1946.

of Jacobson[43] would suggest that the intrinsic factor
produced in the gastro-intestinal tract is a complex con-
taining xanthopterin or a closely related substance, pos-
sibly folic acid. However, the preponderance of evi-
dence indicates that the intrinsic factor is an enzyme
which permits synthesis of the maturation factor by its
reaction with the extrinsic factor contained in, or
closely associated with, the vitamin B complex. What-
ever the detailed mechanism of this reaction, it may
involve the liberation of folic acid from precursors, as
demonstrated by Totter and his associates.[40] It may
also involve conjugation with a protein or an aggre-
gate of amino-acids, or the function of the enzyme may
be the adding of glutamic acid units to the folic acid
molecule to produce the maturation factor stored in the
liver and released as needed for blood formation. Per-
nicious anemia would then represent a cellular atrophy
of those elements of the intestinal tract which are nec-
essary for the synthesizing of dietary materials into
an active form.

An additional clue to the mechanism of action of
folic acid has been provided by Bethell and his asso-
ciates,[44] who have demonstrated an inability of subjects
with pernicious anemia to utilize conjugated folic acid.
Since it is present in foods largely in the conjugated
form, its unavailability for hemopoiesis constitutes the
specific metabolic defect in pernicious anemia. It may
be the function of the maturation factor of liver and

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43 Jacobson, W.: Biochem. J., 40:1, 1946.
44 Bethell, F. H.; Swendseid, M. E.; Brown, R. A.; Meyers, M. C.,
and Andrews, G. A.: Proc. Cent. Soc. Clin. Research (1946), p. 28.
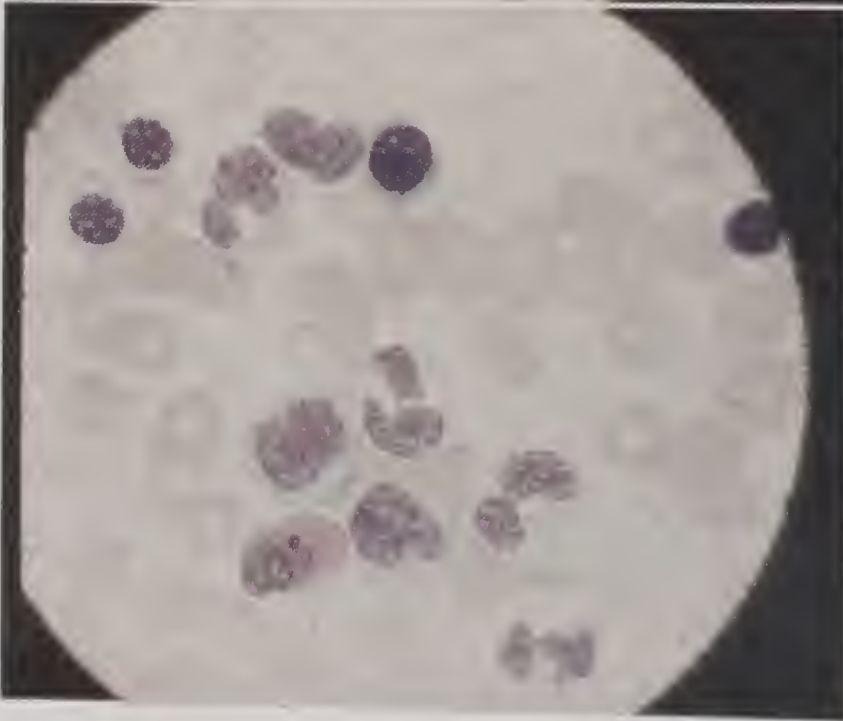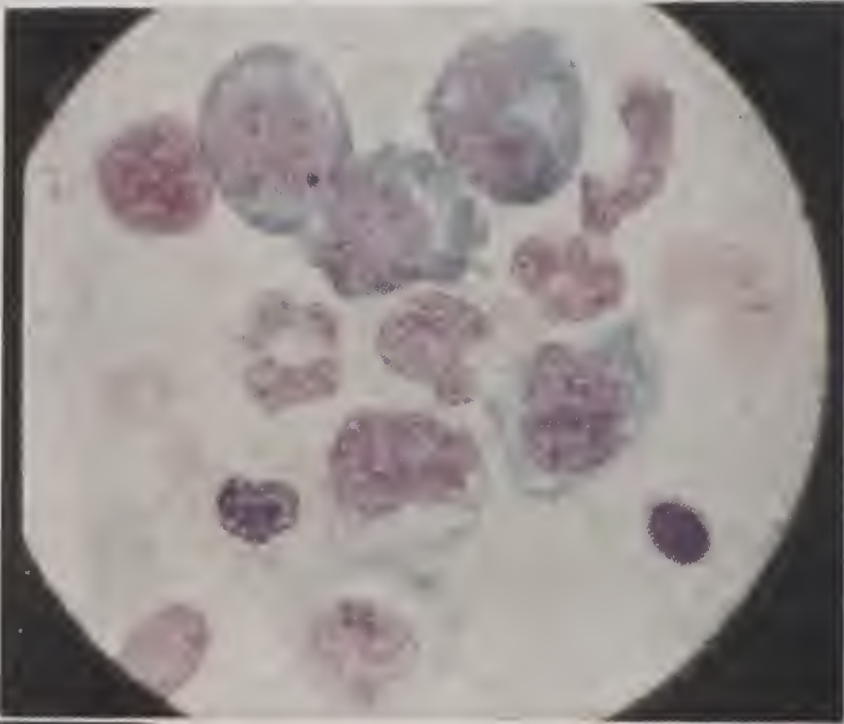
Fig. 31 (above).—Bone marrow before treatment with folic acid. The large cells are megaloblasts; one contains some hemoglobin.

Fig. 32 (below).—Bone marrow after folic acid therapy. The megaloblasts have disappeared and normoblasts are now abundant. Macrocytosis of the red cells has almost disappeared.

liver extract to provide the enzymatic mechanism for the freeing of folic acid from its bound form, after which utilization is possible.

Dosage of folic acid in clinical work has varied from 1 to 500 mg. daily, administered either parenterally or orally. Moore has demonstrated its effectiveness also when administered as an enema. Large doses are unnecessary, for Moore and Bierbaum[45] found that 1 mg. by injection and 3 mg. orally cause nearly maximal responses. The usual dosage is 25-75 mg. parenterally once weekly. Such a program has led to sustained clinical remissions in pernicious anemia. The same dosage is used for all other types of macrocytic anemia. Oral administration of the same doses is also highly effective. Improvement usually appears as early as the third or fourth day and the reticulocyte rise reaches a peak about the tenth day. No adequate information is available on the effect of folic acid on the central nervous system lesions of pernicious anemia, but the accumulating evidence indicates that complete therapy is not provided, for degenerative nerve lesions have been found to progress during folic acid administration. Thus administration of liver preparations is still the treatment of choice for these complications of the disease. The bone marrow arrest is corrected by folic acid, with complete return to normal, as seen in Figures 31 and 32.

Folic acid excretion in the urine of treated patients varies between 9 and 24 per cent of the administered

[45] Moore, C. V., and Bierbaum, O. S.: Proc. Am. Soc. Clin. Investigation (1946), p. 10.

oral dose and between 15 and 75 per cent of the injected dose.[41]

MONKEY ANTIANEMIA FACTOR

Evidence of the existence of an additional factor concerned with normal hemopoiesis rests on observations in monkeys that the experimental production of vitamin B_c or folic acid deficiency precipitates the appearance of an additional deficiency manifested by failure of complete restoration of the blood to normal by addition of folic acid supplements.[46] Folic acid corrects the leukopenia and causes some hemoglobin response, but whole liver is necessary to return the lymphocyte-neutrophil ratio to normal and to obtain a maximal response in hemoglobin regeneration. The principle responsible for this effect appears to be extremely labile, since any type of treatment of liver destroys it.

The bearing of these findings on clinical problems is unknown, but it is possible that the incomplete response of pernicious anemia to synthetic folic acid, which has often been noted, is a manifestation of the human need for this additional factor. If such is the case, the plateau in hemoglobin regeneration which follows the initial dramatic response should be corrected by further supplementation with the monkey antianemia factor or with whole liver which contains it. Clinical work with this substance must necessarily await further clarification of experimental effects in animals.

[46] Cooperman, J. M.; Elvehjem, C. A.; McCall, K. B., and Ruegamer, W. R.: Proc. Soc. Exper. Biol. & Med., 61:92, 1946.

ASCORBIC ACID

Vitamin C, like many of the other vitamins, was discovered through recognition of a deficiency disease. Scurvy has been known since the time when men first began to sail the sea in ships, and it was in connection with voyages of exploration that the condition became most widely recognized. One of the best early descriptions of the disease was that of Jacques Cartier in 1600, in which this explorer related not only the ravages of the disease among seamen but also the miraculous cures effected by the use of infusions of the bark and leaves of the Ameda tree. The first accurate treatise on this subject to appear in the medical literature was apparently that of James Lind, a practitioner of Edinburgh, who in 1753 wrote his famous *Treatise of the Scurvy*. It was largely through the influence of this man and his observations that scurvy was eliminated from the British navy about 1765 through the simple expedient of supplying every ship with an adequate store of lemons. The antiscorbutic potency of citrus fruits and their juices thus became firmly established long before the active constituent of these food materials was discovered.

The isolation of hexuronic (ascorbic) acid was announced 180 years later, in 1932, almost simultane-

ously by Waugh and King in the United States and by Svirbely and Szent-Györgyi in Hungary. The pure material was obtained first from the adrenal cortex of animals and from cabbage leaves, and since that time it has been found widely in plant and animal tissues, in both of which locations it plays an extremely important rôle in a variety of metabolic processes, the nature of which is as yet poorly understood.

The structure of ascorbic acid is shown in Figure 33. This chemical configuration is easily recognized as typical of other well known carbohydrates, from

ASCORBIC ACID   DEHYDROASCORBIC ACID
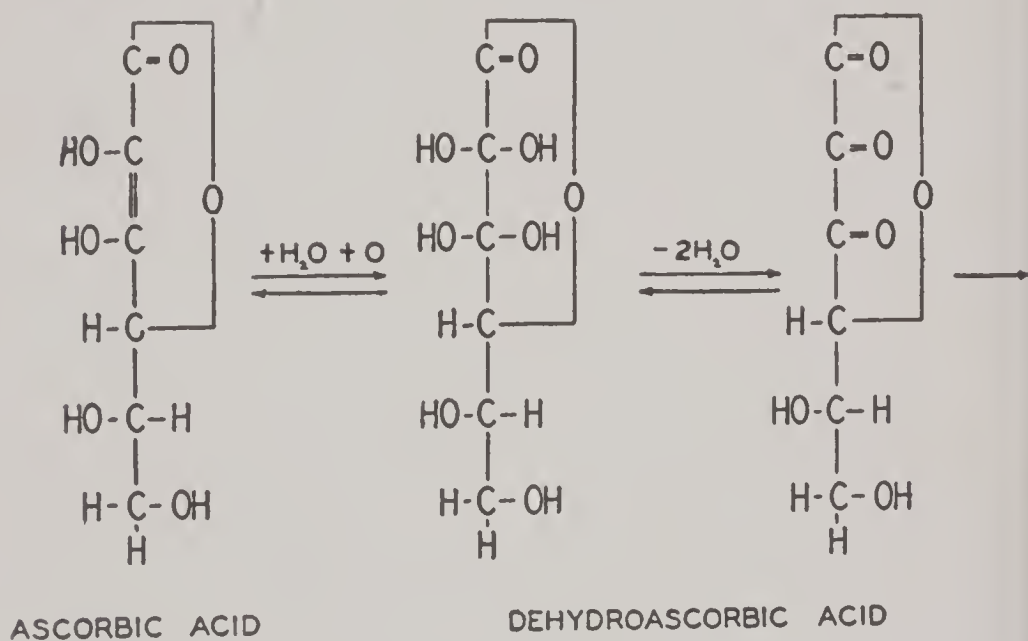
Fig. 33.

which the vitamin is probably derived in biologic systems. The most outstanding chemical characteristic of ascorbic acid is its unusual sensitivity to oxidation. On this fact depends the necessity for excessive care in the preparation and preservation of food materials in order that their antiscorbutic potency

may be retained. This instability is considerably greater when the solution is alkaline. In fact, in acid solutions, ascorbic acid is not oxidized by air unless the reaction is catalyzed by traces of copper.

Of all the animal species studied, only the guinea-pig, the primates and man depend on external sources of ascorbic acid. All other species possess the power of endogenous synthesis in amounts adequate to prevent the development of scurvy, even on an ascorbic acid-free diet, provided metabolism is normal. The most clearly established functional rôle of ascorbic acid which has thus far been defined is that concerned with the maintenance of connective tissues of various types, sometimes termed intercellular substance. This manifests itself most clearly in scorbutic animals in the failure of fibroblasts to form fibers of collagenous connective tissue. It is also apparent in the weakness which this deficiency produces in the walls of capillaries throughout the body, by reason of this same lack of adequate intercellular substance in some as yet unidentified portion of the vascular structure. In the bones, particularly in children, there is a weakness in the attachment of the periosteum, which becomes most prominent at muscular insertions and which frequently leads to subperiosteal hemorrhages. In addition, bone growth ceases, apparently owing to the inability of osteoblasts to form normal bone. They tend to produce a defective type of collagen-poor connective tissue instead, which is most conspicuous in the region connecting the diaphysis with the epiphysis. The teeth are affected because of the resorption

of dentin and the atrophy of odontoblasts, which produce a soft, defective structure which is unusually susceptible to caries formation. The gums are affected only when teeth are present, by a process which causes swelling, sponginess and bleeding. Resorption of bone in the alveolar processes causes loosening of the teeth. Abnormalities of tooth formation have been carefully studied in guinea-pigs fed a scurvy-producing diet, in which a whole blood level of 0.22 mg. per 100 cc. is necessary for the prevention of pathologic dentition.[1] In human beings the health of gum tissues is dependent in a striking way on the ascorbic acid content of the diet. Gingival infection, sponginess and bleeding of the gums may be the only apparent manifestations of a suboptimal intake. In a study of normal healthy adult males an intake of 75-100 mg. daily was found to improve the condition of the gingival tissues and to be reflected in a response of the plasma vitamin C levels.[2] These findings do not mean, of course, that all pyorrhea and gingivitis are due to ascorbic acid deficiency. In the skin a deficiency of vitamin C causes hemorrhages around each hair follicle, particularly on the lower extremities. These lesions are typical and are especially important because they are so accessible to examination and are readily recognized. Scurvy is also accompanied by a variety of other lesions, including degeneration of skeletal muscle, bloody effusions, anemia, cardiac enlargement and endocrine atrophy.

[1] Kuether, C. A.; Telford, I. R., and Roe, J. H.: J. Nutrition, 28:347, 1944.
[2] Kyhos, E. D.; Gordon, E. S.; Kimble, M. S., and Sevringhaus, E. L.: J. Nutrition, 27:271, 1944.

The physiologic importance of ascorbic acid and the consequences of its deficiency have not yet been satisfactorily translated into terms of cellular chemistry. Certain rôles played by this substance have been recognized under experimental conditions. It is well known that certain enzymes and enzyme systems are sensitive to oxidation-reduction conditions in their environments. Presence of an oxidizing agent may completely destroy the activity of such chemical mechanisms. Ascorbic acid, often working in conjunction with other reducing substances, is now known to perform a protective function in a variety of enzyme systems, at least under the conditions prevailing in laboratory experiments. Whether this observation can be applied without reservation to the intact living organism seems doubtful, but the evidence at least suggests that the fundamental position of this vitamin in biologic processes may be represented by some function of this sort. It is also probable, although as yet unproved, that it acts as a carrier of hydrogen in biologic oxidations. Moderately good evidence is also available which suggests that ascorbic acid functions in other enzyme mechanisms. It appears to occupy an important position in the metabolism of some aromatic amino-acids and various important compounds derived from them such as melanin, adrenalin and thyroxin. The activities of certain other enzymes, notably hepatic esterase and serum phosphatase, appear to depend in some manner on this vitamin.

The relationship of ascorbic acid to immunologic

reactions is obscure. Attempts to correlate a deficiency state with diminished antibody production, complement titer and phagocytic activity have been negative. Activation of complement by ascorbic acid seemed to be a good possibility at one time, but it has not been verified. Many reports have appeared on the inactivating effect of ascorbic acid on different viruses in vitro. This relationship, observed long ago for poliomyelitis virus, has been corroborated by Knight and Stanley,[3] for influenza A virus. The immediate cause of the effect, however, appears to be the production of hydrogen peroxide in the reaction, since catalase abolishes the inactivation. Because of the abundance of catalase in animal tissues, it appears doubtful that this phenomenon can have any practical application in therapy.

No final or satisfactory interpretation has yet been made of the unusually high concentration of ascorbic acid known to exist in the pituitary gland, adrenal cortex, corpus luteum of the ovary and other tissues of high metabolic activity. In all of these sites it is highly probable that the presence of ascorbic acid is correlated with the chemical processes involved in the hormone syntheses in the various glands, but the manner in which this occurs is not clear. It is well known that human patients with adrenal insufficiency show signs suggesting ascorbic acid deficiency, and there is also evidence that the content of both ascorbic acid and cortical hormone in the adrenals of scorbutic guinea-

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[3] Knight, C. A., and Stanley, W. M.: J. Exper. Med., 79:291, 1944.

pigs is very low. Sayers and his co-workers[4] have shown that the response of rats to injection of pituitary adrenotropic hormone involves an immediate fall in both ascorbic acid and cholesterol content of the gland, with a return to normal in a few hours. These observations may tentatively be interpreted as indicating the participation of both in the synthesis of the cortical hormone. Much more information is urgently needed before the chemistry of hormone production can be understood, nevertheless the occurrence of high concentrations of ascorbic acid in areas of high metabolic activity is certainly no coincidence; this is a general biologic phenomenon seen regularly in plants and in animals.

Food Sources and Human Requirements

Citrus fruits are well recognized as the most concentrated common sources for this vitamin. There are many other excellent sources, however, which are shown in Table 10. It is apparent from these figures that the best sources in ordinary diets in addition to citrus fruits are green leafy vegetables, tomatoes and berries; meats of all types contain negligible amounts of ascorbic acid.

The effective ascorbic acid content of the diet and of any single food constituent depends on two factors which are apparent from a consideration of the chemical nature of this compound. (1) The original anti-scorbutic potency of the food in its original unprocessed state determines the maximum values. (2)

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[4] Sayers, G.; Sayers, M. A.; Lewis, H. L., and Long, C. N. H.: Proc. Soc. Exper. Biol. & Med., 55:238, 1944.

TABLE 10.—Ascorbic Acid Content of Foods*

	Mg. per 100 Gm.
Apples	5
Bananas	10
Blueberries	16
Strawberries	60
Cantaloupe	33
Grapefruit	40
Lemons	45
Oranges	49
Pineapple	24
Tangerines	31
Grapefruit juice, canned	35
Grapefruit segments, canned	30
Orange juice, canned	42
Asparagus	33
Beans, green lima	32
Beet greens	34
Broccoli	118
Brussels sprouts	94
Cabbage	52
Cauliflower	69
Peppers, green	120
Spinach	59
Turnip greens	136
Tomatoes, fresh	23
Tomatoes, canned	16
Tomato juice, canned	16
Tomato purée, canned	28
Spinach, canned	14
Asparagus, canned	15

* These figures are from the Tables of Food Composition prepared by the Bureau of Human Nutrition and Home Economics, in co-operation with the National Research Council, U. S. Department of Agriculture, Miscellaneous Publication no. 572 (1945). Nutritive values are given for foods as brought into the house for consumption; no account has been taken of losses of food value that may occur in preparation of meals.

The manner of preparation from the raw state determines the losses before consumption. This may be divided into six details. The first is the acidity or alkalinity of the medium. Ascorbic acid is more stable in acid solution, and for this reason adding of baking soda to the food or otherwise increasing the alkalinity usually results in a substantial loss in potency. Second, to a large extent the temperature controls the rate of ascorbic acid oxidation. Food should be kept

refrigerated at all times until it is cooked or con-
sumed. Third, there is some evidence that antiscor-
butic potency is retained more effectively when the
food is kept in the dark, i.e., away from sunlight.
Fourth, the availability of oxygen is of the greatest
importance. Boiling or stewing of food with con-
stant stirring to effect maximum oxygenation rapidly
destroys the entire ascorbic acid content. Anaerobic
heating, on the other hand, results in practically
no loss. Fifth, copper has a destructive effect. This
element has been shown to catalyze the oxidation
of ascorbic acid. Contact with copper in cooking
utensils should therefore be avoided as far as possi-
ble in the preparation of food. Sixth, the time elapsed
between harvesting and consumption of food should
be as short as possible. While some foods retain their
vitamin potency for a long time, this is by no means
a general rule. Oxidation proceeds slowly even under
the best of conditions.

Destruction of ascorbic acid, as well as other heat-
labile vitamins in the process of cooking, may be re-
duced to a minimum by observation of the foregoing
details. Since in many vegetables specific enzymes
exist for the oxidation of ascorbic acid, it is distinct-
ly advantageous to have the water in which these
vegetables are cooked at a boiling temperature before
they are added. This inactivates the enzymes, speeds
up the entire cooking process and minimizes destruc-
tion by oxidation. However, cooking loss of antiscor-
butic activity may still be relatively great owing to
the usual practice of discarding the cooking water in

which a large part of the vitamin has been dissolved. Pickling, salting, curing, fermenting and leaching all result usually in nearly complete loss, while freezing and drying are consistent with a retention of good potency. Both quick freezing and pressure cooking of foods are effective in preserving their vitamin C potency. The latter process is best carried out in as short a time as possible and with a minimum amount of water.

The efficacy of milk in supplying ascorbic acid is of some interest. Raw whole cow's milk usually contains 25-30 mg. per liter, according to the older accepted figures. This amount would go far toward supplying the needs for a normal adult for one day were it not for the fact that most of the commercial milk supply is pasteurized. Pasteurization, particularly by the older methods, consists of heating the milk to a temperature of about 154 F., with no attempt made to exclude air. By this process about half of the original ascorbic acid content of the milk is destroyed. Human milk contains approximately four to six times as much of this vitamin as does cow's milk, and there is usually no opportunity for loss before consumption, so occurrence of scurvy among breast-fed infants is negligible.

In a recent study Stewart and Sharp[5] found the ascorbic acid content of raw cow's milk to be about 17 mg. per liter. The figures for pasteurized, evaporated (reconstituted) and fresh powdered whole milk (reconstituted) were 5.8, 2.0 and 12.5 mg., respectively. Stor-

5 Stewart, A. P., and Sharp, P. F.: J. Nutrition, 31:161, 1946.

age of powdered milk led to losses of 11.3, 14.5 and 20.2 per cent after three, six and 12 months, respectively.

Repeated investigations of the antiscorbutic potency of orange juice have revealed a lack of uniformity in content of fruit grown in different parts of the country. These figures vary from 40 to 65 mg. per 100 cc. of the juice. Since one orange may contain from 60 to 100 cc. of juice, it is apparent that one orange per day will usually supply nearly the adult optimum daily requirement. Although grapefruit, lemon and tomato juices are also potent sources of this vitamin, under ordinarily prevailing prices orange juice is the cheapest form in which to obtain ascorbic acid. All of these fruits, if stored intact at ordinary refrigeration temperatures (40-50 F.), will still have about three fourths of their original potency after a year. However, the juices of these fruits lose their potency rapidly when left standing at room temperature in the open air, so that half of their antiscorbutic value will be lost after three to four hours. Even under refrigeration conditions these juices lose a substantial proportion of their potency if exposure to air is not restricted. Canned juices, if prepared by the best methods, will retain up to 90 per cent of their original potencies, and they are almost as inexpensive as fresh juices.

The optimum daily ascorbic acid requirement of normal healthy adults has been estimated by a variety of methods, most of which point toward a value which lies between 50 and 75 mg., with a definite tendency toward the latter figure. The National Research

Council recommends 75 mg. for men and 70 mg. for women. Some estimates have even suggested 125 mg. This wide disagreement arises partly from failure to establish a minimal blood level consistent with optimal health. Thus a considerably larger intake is necessary to maintain a blood content of 1 mg. per 100 cc. of blood than to keep it at 0.8 mg. On the basis of all available evidence, it is probably justifiable to accept 75 mg. as a critical level of intake below which manifestations of mild deficiency are likely to appear. Infants under 1 year probably need 30-35 mg. daily at a minimum, with an optimal figure at least three times this. Growing children between 4 and 12 require 50-75 mg. daily and should probably receive the same amounts as adults. Pregnancy is attended by abnormally high demands which must be met by an optimal intake of at least 100 mg. daily. The National Research Council recommends 100 and 150 mg. as the daily intake for pregnancy and lactation, respectively. Many different conditions increase the need for ascorbic acid, but particular mention should be made of those attended by a general rise in metabolic activity, such as severe infections, thyrotoxicosis, severe exercise and fevers from all causes. In certain circumstances, in addition, absorption of the vitamin from the gastro-intestinal tract is impaired, resulting in mild deficiency manifestations. It is apparent that the exact cause must first be identified in any given case so that therapy may be directed toward the underlying process as well as toward the deficiency itself.

Blood ascorbic acid levels of new-born infants are

almost invariably higher than those of the mother.
With very low levels in the mother, the infant's blood
may be five to 10 times higher, while in the optimal
maternal range, this difference is much less striking.
The interpretation of these findings indicates the pres-
ence of a mechanism probably residing in the placenta
which insures an adequate supply of ascorbic acid to
the fetus at all times. A scorbutic infant on delivery
would therefore be a rarity and would necessitate the
mother's being in a serious nutritional state indeed.
Lund[6] has shown that complications in pregnancy, es-
pecially infections such as pyelitis, cause a sharp lower-
ing of maternal blood levels. The fetus, however, may
continue despite these conditions to extract the needed
ascorbic acid from maternal tissues. Thus, scurvy in
an infant during either the intra-uterine or the neonatal
period is a rarity, despite the fact that the fetal drain
superimposed on an inadequate intake may have se-
riously depleted the mother's reserves so that she has
no protection against emergencies.

In the chemical determination of ascorbic acid in
biologic materials, use is made of the strong reducing
power of this substance, through the use of the dye
2: 6-dichlorophenol-indophenol, which is changed to
a colorless compound by the action of the vitamin. The
pitfalls known to complicate this technic are of the
greatest importance, since the presence of other re-
ducing substances in blood and urine leads to errone-
ous high results. Particularly troublesome are the
various sulfur-containing compounds which are al-

[6] Lund, C. J.: J. A. M. A., 128:344, 1945.

ways abundant in urine. Nevertheless certain technics have been worked out to make possible more accurate estimations of blood and urine values. Estimations on the blood are probably the more important for clinical purposes and also more accurately determined, since relatively few interfering substances are present in blood.

Mention should also be made of the method using dinitrophenylhydrazine for the production of a colored hydrazone which can be measured. This method has been shown to be nonspecific and therefore less reliable, especially for the analysis of animal tissues.

By means of a method employing decolorization of the indophenol dye and subsequent measurement in a photoelectric colorimeter the ascorbic acid content of blood serum of normal healthy adults is usually found to exceed 0.8 mg. per 100 cc. of blood. From this level down to zero, suboptimal intake of vitamin C may be assumed to exist, and under scorbutic conditions the blood is almost regularly shown to contain no demonstrable ascorbic acid. The vitamin is present in greater concentration in the layer of white cells and platelets obtained by centrifugation, and in deficiency states its presence may be demonstrated by this means long after it has completely disappeared from plasma. Therefore, since white cells and platelets contain ascorbic acid at the expense of plasma and retain it tenaciously in much the same manner as do tissue cells, analysis of these fractions of blood is most important in the evaluation of serious deficiencies. By contrast, because plasma is the first component to be depleted in deficiency and the

last to return to normal during restoration, plasma determinations are of greater significance in the estimation of degrees of saturation and the identification of grades of suboptimal intake. Although all of these determinations are technically exacting, that of plasma is much the simplest and, if interpreted properly, is of great value clinically.

It is noteworthy that the results obtained by these methods often do not parallel the tourniquet, Göthlin or Rumpel-Leeds tests for capillary fragility. The last is being found definitely undependable as a criterion of vitamin C nutrition when checked against the better chemical methods. Urinary excretion fluctuates widely depending on the intake, since this vitamin acts as a threshold substance. Excretion may fall to zero in severe deficiency and may rise to quantitative levels under conditions of saturation. Saturation tests have been proposed to permit evaluation of body stores. These may be of definite value in the future, but so far no uniform technic has been adopted, and the exact value of the information so obtained remains unsettled. It seems worthy of emphasis that there is a conspicuous lack of correlation between the blood changes and the clinical manifestations of ascorbic acid deficiency. Not only may blood levels of zero be found in subjects who obviously do not have clinical scurvy, but persons with full-blown scurvy may show from traces to small measurable amounts of ascorbic acid. These facts accentuate the uncertainty regarding mild, latent or subclinical states in subjects with a demonstrable suboptimal dietary

intake. Supported by the findings in experimental human scurvy, described below, these facts also lead logically to the belief that the naturally occurring disease as presented in classic descriptions must certainly be a more complicated condition than simple ascorbic acid deficiency.

Scurvy.—Experimental production of human ascorbic acid deficiency has done much to provide a helpful new perspective of the whole problem of clinical scurvy. It now appears that the period of tissue depletion prior to the appearance of the usual, recognized manifestations, must be much longer than had previously been realized. In one carefully performed study,[7] the first clinical evidences of deficiency appeared 134 days after the experiment began, after the plasma ascorbic acid level had been zero for 93 days. Typical perifollicular hemorrhages in the skin were first noted in 161 days and sterile skin incisions first showed delay in healing in 182 days, at which time the diet was discontinued. Bleeding gums were not noted at any time during the experiment, nor was the Rumpel-Leeds test ever positive. These observations seem to be at variance with older reports of ocean voyages during which full-blown or even fatal scurvy developed in 60 to 120 days. The presence of other coexisting deficiencies may provide the explanation.

By means of biomicroscopic examination, Kruse believes he can detect anatomic changes in the gums in early ascorbic acid desaturation. These lesions consist of enlarged, congested capillaries, redness of the

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[7] Lund, C. C., and Crandon, J. H.: J. A. M. A., 116:663, 1941.

Fig. 34.—Child with scurvy. Position is typical of scurvy in infants. Note petechial hemorrhages over skin surface.

Fig. 35.—Mouth of child with scurvy. Swollen and spongy gums. Soft tissues nearly obscure teeth in places; one bleeding point visible.

Fig. 36.—Scurvy just beginning to heal. There is "ground glass" osteoporosis of all bones. Large subperiosteal hemorrhages around both femurs sharply outlined, and indicated externally by soft tissue swelling. Note lateral displacement of distal femoral epiphysis at left.

gum, followed by swelling, usually appearing first in the upper gum in the interdental papillae. Many of the changes can be seen without the aid of a microscope. It is interesting that in many subjects with blood ascorbic acid levels of 1 mg. per 100 cc. or higher these lesions have been found, and according to chemical criteria they could not be considered to be deficient. Such findings can only mean that tissue changes of avitaminosis are corrected so slowly by dietary supplements that they fail to reflect brief changes in vitamin intake detectable by chemical methods. Further experience of clinicians interested in the problem of diagnosis of borderline deficiency states will eventually establish the validity and dependability of these observations.

Scurvy is still seen in children with surprising frequency despite the wide general dissemination of knowledge regarding vitamins in the last few years. For obvious reasons it is much more prevalent in artificially fed infants than in those receiving breast milk. Outstanding among the clinical signs is the characteristic position assumed by the infant in bed. The flexion, wide abduction and external rotation of the legs are shown in Figure 34. This position is probably largely due to the extreme pain produced by the subperiosteal hemorrhages, which are most likely to occur around the bones of the lower extremities. Blood may also infiltrate the muscles and the cellular structures surrounding the joints. Despite this, the joints themselves are rarely affected. The gums are swollen and red and may almost cover the teeth (Fig.

35). The child cries with almost no provocation, but particularly in response to handling or to jarring or moving of the bed. Examination of the blood shows either a complete absence of ascorbic acid or a markedly reduced level. Moderate secondary anemia is regularly present, with hemoglobin levels in severe cases as low as 30-40 per cent of normal. Hemorrhages may occur from almost any of the mucous membranes.

Great interest has been stimulated by a series of observations on the anemia of scurvy. Vilter and Woolford[8] described a normocytic or mildly macrocytic anemia, with some suggestion of a hemolytic factor in pathogenesis, observed in a group of patients with clinical scurvy. Reticulocyte responses of 5 to 19 per cent occurred on the fifth or sixth day after daily administration of 500 mg. of ascorbic acid while the patients were being maintained on a low B complex diet. Gottlieb[9] reported several similar instances of hyperchromic macrocytic anemia which also responded to ascorbic acid, but the basal diet was not controlled. Even pernicious anemia of the classic type has been shown to respond to supplements of this vitamin in individuals who had not improved on liver therapy.[10] Thus the exact way in which ascorbic acid fits into the well established mechanism for the development of macrocytic anemia seems quite obscure. At least it appears that anemia is a common manifestation of

8 Vilter, R., and Woolford, R. M.: Proc. Central Soc. for Clin. Research, 17:34, 1944.

9 Gottlieb, B.: Brit. M. J., 2:119, 1945.

10 Dyke, S. C.; Della Vida, B. L., and Delikat, E.: Lancet 2:278, 1942.

scurvy, and the total functioning of the hemopoietic system may possibly prove to be dependent in some specific detail on an adequate supply of ascorbic acid.

In adult patients, subperiosteal hemorrhages are seldom seen, but there are many petechial hemorrhages into the skin, especially that surrounding the hair follicles. Bleeding into the muscles causes brawny tender swellings. Bloody diarrhea is not uncommon. Bleeding gums, extravasation into the mucous membranes and secondary anemia are found as in children. Blood ascorbic acid levels are usually zero.

The incidence of classic scurvy in this country is fortunately low, but the occurrence of borderline or subclinical states is remarkably common. Students of nutrition are not prepared to state, on the basis of quantitative studies, what the consequences of this suboptimal level of nutrition will be, in terms of physical disability, but as in the case of other vitamins it probably has a tendency to impair the general state of health. Studies of experimental scurvy have revealed no tendency to increased fatigue or to diminished physical or mental efficiency, but this might not be true in multiple deficiency states, in which a lack of ascorbic acid is only one of many defects. Clinical scurvy in its severest form is not difficult to recognize, but the mild cases without striking external manifestations are by no means easy to identify. Laboratory assistance is often indispensable.

Hemorrhagic diseases.—The prompt response of the petechial hemorrhages in scurvy to the administration of adequate doses of ascorbic acid naturally led

to the trial of this substance in various of the other hemorrhagic diseases such as Schönlein's and Henoch's purpuras, hemophilia and idiopathic thrombocytopenic purpura. Critical clinical studies have been uniformly disappointing, however, except in those rare instances in which a hemorrhagic tendency caused by ascorbic acid deficiency coexists. Nevertheless, a study of the nutritional status of every patient with one of the diseases of this group is always indicated, preferably with laboratory studies of ascorbic acid when possible.

Anemia.—While a deficiency of ascorbic acid does not rank in importance with iron deficiency as a cause of anemia, it may nevertheless be a contributing factor in a good many cases. There is good experimental evidence that vitamin C has a specific effect on hematopoiesis, so that the anemia resulting from a lack of this factor is due to defective blood formation rather than to hemorrhages, although in severe cases the latter may also be a contributing cause. This matter has already been discussed.

Dental Caries.—The responsibility of ascorbic acid deficiency in the production of dental caries is a question on which little careful experimental evidence has thus far been brought to bear. It does seem clear, however, that the presence of adequate amounts of this substance is vitally important to the integrity of the forming and growing tooth. Defective structure produced at this time may be responsible for serious dental disease later in life, even though the diet is more satisfactory during the adult years. The

function of vitamin C in maintaining healthy gums is also apparent from the well known abnormality of these structures in scurvy. The exact effect of border-line deficiency on the entire dental and accessory structure is not positively known, since evidence on this point is difficult to obtain.

Other Conditions.—Ascorbic acid has been used in the therapy of many pathologic states in which good evidence exists to justify its administration. On the other hand, it has often been used equally freely without good reason. In achlorhydria and in severe chronic diarrheas of various types, the absorption of ascorbic acid is impaired, in the first instance probably owing to the lack of protection from oxidation usually provided by gastric acid and in the latter case owing to the increased intestinal rate. In both of these conditions proper therapeutic measures in addition to moderate supplements of the vitamin will bring about a restoration of normal body stores.

Peptic ulcer diets of the Sippy type are usually low in ascorbic acid. When this fact is superimposed on the probability of a preexisting inadequacy of this vitamin as well as many others, it seems reasonable that more than an average intake of ascorbic acid should be regularly provided to ulcer patients. To that end it is common practice in many clinics to include orange juice several times daily as a part of the Sippy ulcer regimen. Chemical studies on the blood and urine of ulcer patients have actually demonstrated this deficiency, and it is perhaps more than coincidence that the lowest figures are usually obtained in

those individuals who are or have been bleeding. The mechanism by which this bleeding occurs is not clear, since it usually involves the larger vessels, injury to which is not usually considered to be associated with this deficiency. The poor protein intake of most patients with peptic ulcer may be an important contributing factor.

The pigmentation of Addison's disease is probably due to a disturbance in the metabolism of melanin which is at least partially controlled by the adrenal gland. A part in this process has been attributed to ascorbic acid which is normally so abundant in this tissue. This belief led to therapeutic trial of the vitamin in an attempt to control the pigmentation, but results have been rather disappointing. While there have been some encouraging reports, for the most part these attempts have not been successful despite the use of large doses over many weeks. It must be admitted that the functional rôle of ascorbic acid in relation to the adrenal cortex is poorly understood.

Ascorbic acid has a logical field of usefulness in the management of chronic infectious conditions. Particular mention should be made of tuberculosis, osteomyelitis, rheumatoid arthritis and rheumatic fever, in all of which the blood levels have been found consistently low and the body stores depleted. It is quite probable that both this depleted state and the difficulty frequently seen in restoring normal values by means of a long-continued high intake are merely a reflection of the elevated metabolism incident to an infectious process operating continuously over a long period.

The same point of view is equally applicable to thyrotoxicosis. If this vitamin does have any important function in maintaining the immunologic defense mechanisms at top efficiency, it would seem only reasonable that some benefit might be anticipated from the administration of ascorbic acid in amounts adequate to insure good nutritional status. Other vitamins may be as important as vitamin C, but quantitative studies are lacking on which to base a final opinion.

Hypovitaminosis C appears to promote the manifestations of sensitivity to arsenical drugs. As a logical sequence to this finding, the administration of ascorbic acid has been helpful in preventing and curing this condition, although maintenance of a high blood level of the vitamin is often necessary. It is important that the arsenical drug and the ascorbic acid not be given together, since some of the arsenicals are actually precipitated by vitamin C.

Space does not permit discussion of all of the conditions in which ascorbic acid has been used as a therapeutic agent. Mention may be made, however, of some of these diseases, e. g., acne vulgaris, lead poisoning, lupus erythematosus, acute coryza, chronic sinusitis, diabetes mellitus, allergies of all types, progressive muscular dystrophy, defective healing of surgical wounds and a score of others. In passing judgment on any form of nutritional therapy in a list of diseases of this sort, emphasis should again be placed on the quantitative aspect of vitamin action in general, since the best available evidence fails to attribute therapeutic effectiveness to vitamin admin-

istration except in the presence of a deficiency. If evidence of such a deficiency exists, therapy is certainly indicated. Attention should again be called to the frequent necessity for prolonged treatment of avitaminosis C, especially the chronic deficiency states with stubborn tissue changes, in which an excessive supply of ascorbic acid to all tissue cells seems to be required for long periods after storage capacity has been filled.

The Council on Foods and Nutrition of the American Medical Association[11] recommends treatment of acute vitamin C deficiency states with 100 mg. or more daily for weeks. For chronic conditions the suggested dosage is 100 mg. three times daily for an indefinite, prolonged period, depending on the rate of improvement.

In all the field of medicine there is probably no more dramatic or gratifying result from a therapeutic measure than that which occurs when a patient with scurvy is given an adequate amount of ascorbic acid. Most of the clinical manifestations disappear with astonishing speed. Resorption of hemorrhages in the tissues unfortunately requires considerable time and may be hampered by metastatic calcification.

Vitamin P

This term is the alphabetical designation assigned to a factor occurring in close association with ascorbic acid and thought to have an antihemorrhagic effect through its action on capillaries. This substance, known also as citrin, has been identified chemically

11 J. A. M. A., 131:666, 1946.

as eriodictyol. Another closely related compound with similar properties is known chemically as hesperidin; both have been studied as possible nutritional factors, the absence of which might explain the hemorrhagic tendency in scurvy, usually attributed to ascorbic acid deficiency. Several clinical studies have appeared reporting favorable results in the treatment with vitamin P of cases with hemorrhagic tendency from such diverse causes as arsenical therapy, measles and thrombocytopenic, nutritional, allergic, infectious and mechanical purpuras. Most of these reports have appeared in foreign journals. Dosages used have varied up to 150 mg. daily by the oral route of a mixture of eriodictyol glucoside and hesperidin. However, these investigations are inadequately controlled, and there is consequently no dependable evidence from either animal or clinical experimentation to justify regarding vitamin P as an indispensable factor in nutrition. Indeed, with the increased scope of these clinical trials and the perspective provided by the passage of time since these materials first appeared, it may be stated without reservation that hesperidin and eriodictyol, at least, do not possess the antihemorrhagic potency nor the therapeutic value originally ascribed to them.

A new vitamin P substance, called "rutin," is closely related chemically to the other compounds. Its structure is shown in Figure 37. It is a glucoside derived from buckwheat leaves and blossoms, tobacco leaf, tomato stems, white hydrangeas, yellow pansies and elderberry leaves. It is possible, although not proved,

that the physiologic activity originally attributed to the crude "citrin" glucosides was, in reality, due to the presence of rutin. The compound is nontoxic for man and has been found in preliminary trials to increase capillary resistance in a number of hemorrhagic conditions. One report[12] has pointed out its efficacy in re-
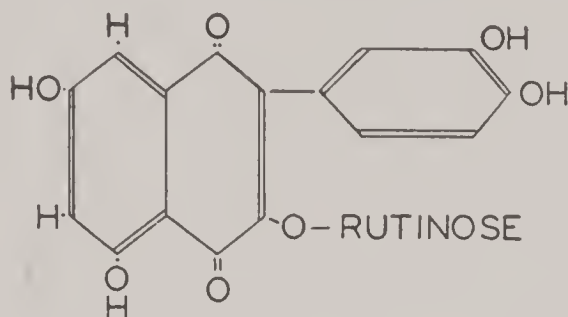
Fig. 37.—Rutin.

ducing the incidence of hemorrhages in hypertension, the capillary fragility in drug reactions and the bleeding tendency in other poorly defined hemorrhagic states. It has no effect whatever on the hypertension itself, and even its effectiveness in the conditions listed must be accepted with great reservation until an abundance of controlled observations is available. Another report,[13] on the influence of rutin on purpura associated with allergic, malignant and other miscellaneous conditions, gives some hope that this substance will be useful. Best results were obtained in the malignant group, less convincing results in the allergies and questionable effects in the other cases.

12 Shanno, R. L.: Am. J. M. Sc., 211:539, 1946.

13 Madison, F. W., and Pohle, H. W.: Proc. Cent. Soc. Clin. Research (1946), p. 29.

CHAPTER IX

VITAMIN D

The disease, rickets, must have been known to the human race for many centuries before it was finally accurately described in the medical literature by Whistler in 1645. Indeed, the antiquity of the disease is substantiated by the identification of the skeletal deformities which have been obtained for study through archeologic investigations. The importance of exposure to sunlight as a preventive measure has been emphasized since 1890, but not until 1921 was rickets definitely recognized as a deficiency disease, by Mellanby. Four years earlier, Hess had demonstrated the prophylactic value of cod liver oil in preventing rickets. Ergosterol has been known since 1811, but the possibility of activation was not discovered until 1924. Thus, our knowledge of the chemistry and physiology of vitamin D has been elucidated chiefly during the last decade and a half. Despite the interest this problem has attracted, there are still many phases of the subject which are little understood.

At least 10 distinct chemical compounds are known to possess vitamin D potency. Most of these are of theoretic interest only, but two, calciferol and activated dehydrocholesterol, are of practical importance because of their application to the relief of vitamin

D deficiency in man. Each of these compounds has a corresponding inactive precursor on which potency is conferred by either chemical or physical means. Thus ergosterol, when activated by ultraviolet light, either in the animal body or outside, is converted into
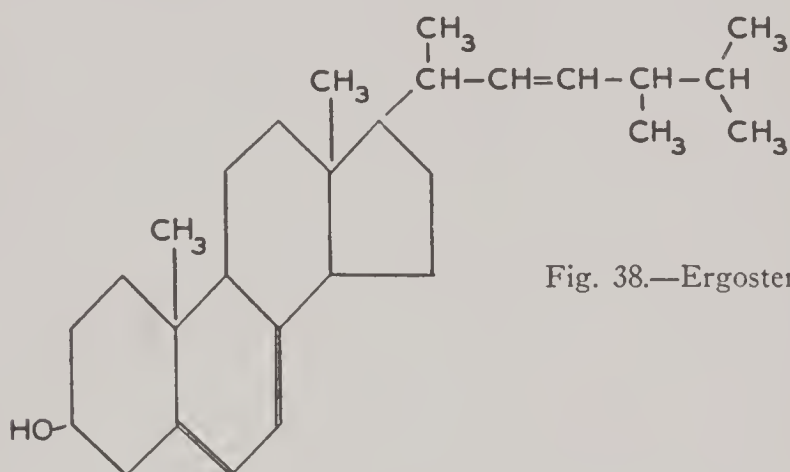
Fig. 38.—Ergosterol.
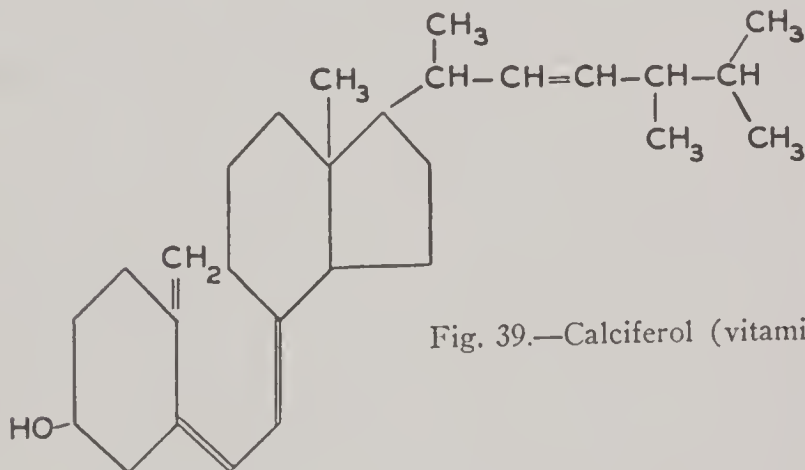
Fig. 39.—Calciferol (vitamin D₂).

calciferol (known medically as viosterol), or vitamin D₂. This conversion is not as simple as it might appear, since several intermediate, biologically inactive stages are known to occur. In a similar manner, dehydrocholesterol, a normal constituent of the natural oil of the skin, is activated by exposure to ultraviolet

irradiation with the production of a substance with antirachitic potency, called vitamin D₃. This latter form is found in fish liver oils, in animal fats and in eggs and represents probably the chief antirachitic compound in animal nutrition. Calciferol, on the other hand, outside of its occurrence in irradiated yeast, is of importance principally because of the concentrated potency which can be artificially prepared through irradiation of ergosterol for treatment of clinical rickets in humans. The present international unit is 0.025 µg. of pure calciferol.

The series of compounds to which the various substances with vitamin D activity belong are generically classified as sterols, the biologic importance of which has only quite recently been fully appreciated. Other important members of the group are the sex hormones, both male and female, the adrenal cortical hormones, some alkaloids such as morphine, some cardiac poisons such as strophanthin, some toad poisons, bile acids and most of the carcinogenic agents. The remarkably similar structures of these various compounds account for the equally slight variability in physical and chemical properties. They are all quite uniformly insoluble in water, slightly to moderately soluble in fats and oils and very soluble in organic solvents such as ether, acetone and chloroform.

The discovery by Steenbock and independently by Hess in 1924 that irradiation of food products of various types would increase their antirachitic potency led to an intensive study of the details of photo-activation. The specific wave band which is responsi-

ble for conferring this activity lies between 2,300 and 3,050 angstroms, with a maximum between 2,800 and 3,050 (peak at 2,967 angstroms) and some activity identified with small bands on either side of this region. Since the visible spectrum occupies the band between 3,900 and 7,400 angstroms, it is apparent that this band of activating energy lies considerably below visibility, in the ultraviolet region. Activation of ergosterol in this region is most effective when the sterol is in solution, preferably in a thin film, and is least efficient when the solid substance is irradiated. In the activation of dehydrocholesterol in the skin, it is well established that the penetration of these wavelengths is slight, and it therefore seems probable that the inactive sterol is located on the skin surface and then absorbed after activation as the compound that is now recognized as vitamin D_3.

The question of the origin of vitamin D potency in the liver oils of fish has been repeatedly raised, but there has never been a completely adequate explanation. It has been suggested that it represents the activity ingested by larger fish when they eat smaller ones, the ultimate source being the plankton food of the smallest marine animals. Generally speaking, vitamin D has been found to be rarely, if ever, produced by living plants, and investigations of the activity of plankton has failed to substantiate this suggestion. On the other hand, it has been equally well shown that direct irradiation of the skin surface of fish plays no part in this process. It therefore appears most likely that the occurrence of these sterols in high

concentration in the livers of fish represents true synthesis by the organism.

The occurrence of vitamin D is limited almost entirely to animal sources, since no living plant tissue is known to contain this substance. Natural foods which contain significant amounts of vitamin D are of animal origin. First in importance are the various fish which contain large amounts of oils, such as sardines, salmon, herring, halibut and cod. Eggs are fairly good sources; milk is of value because of the potency contained in the fat. Animal fats contain appreciable activity but can hardly be considered as good sources. Table 11 shows assayed potencies for common foods.

TABLE 11.—VITAMIN D CONTENT OF FOODS

Foods	I. U. PER 100 GM.
Butter, average	80
Butter, cows on dry feed	40
Butter, cows on pasture	150
Liver, chicken	55
Liver, beef	45
Liver, calf	10
Liver, lamb	17
Liver, pig	44
Clams	5
Eggs	15
Egg white	0
Egg yolk	45
Milk, whole	2
Milk, average market	2
Milk, cows on dry feed	1
Milk, cows on pasture	4
Oysters	5

Such a list illustrates how few natural foods contain significant amounts of vitamin D.

Particular interest has centered about the potency of milk and the practical possibility of fortifying it by irradiation. This special interest is based on three considerations: (1) milk constitutes almost the sole

food for infants over many months during which susceptibility to rickets is maximum; (2) milk is one of the best food sources for calcium and phosphorus, with which the physiology of vitamin D is inseparably bound; (3) the fat of milk contains the necessary sterols for effective activation by irradiation.

There are four approved methods for accomplishing this increase in antirachitic potency of milk. First, the cows may be irradiated with ultraviolet light. The efficiency of this method depends to a certain extent on the breed of cattle, but the maximum potency reported from this procedure is 43.8 I. U. per qt. Second, direct fortification may be effected through the addition of vitamin D concentrates to the milk. There is theoretically no limit to the potency which may thus be attained, but standardization has been stabilized at 400 I. U. per qt. Third, fresh milk may be irradiated. The Council on Foods of the American Medical Association has approved milks prepared in this way when the potency is 135 I. U. per qt. Fourth, vitamin D concentrates may be fed to the cows. The product from such cows is designated "metabolized vitamin D milk," and its accepted standardized potency is 400 I. U. per qt. There is every reason to believe that fortification of milk by any of these processes is equally satisfactory and that unit for unit they all have the same antirachitic potency.

It is both interesting and important that augmentation of vitamin D potency of milk by the feeding of concentrates to the cow is difficult. Quantitative studies have shown that only between 1 and 2 per cent of an

administered dose appears in the milk, so that large supplements must be used to increase the potency of milk sufficiently to be of practical value.[1] This is also true of human milk, as demonstrated by Polskin and his co-workers,[2] who found that doses of 30,000-40,000 units daily to the mother were necessary to produce milk concentrations of 125-580 units per liter. The addition of these supplements during labor or lactation was somewhat more effective than their feeding during pregnancy.

Milk is the only food whose fortification is approved by the Council on Foods, but it is possible to enhance by irradiation the vitamin D content of any food which contains vitamin D precursors. During the early days of this technic, dozens of food products and even cigarets were irradiated, but at present most of these fortified preparations are off the market. Cereals, margarine and a few others remain.

The vitamin D requirement for a normal healthy adult human has been difficult to determine accurately. This is undoubtedly due chiefly to the fact that adults derive most of their supply through ultraviolet irradiation of the skin and also to the lack of any satisfactory criterion of deficiency. In addition to this, the D requirement is minimum when the calcium-phosphorus ratio is 1.2:1 and increases as this ratio rises. Whereas the required intake for infants was formerly set at 400 I. U. daily and that of adults at some

[1] Krauss, W. E.; Bethke, R. M., and Wilder, W.: J. Dairy Sc., 16:549, 1934.

[2] Polskin, L. J.; Kramer, B., and Sobel, A. E.: J. Nutrition, 30:451, 1945.

indefinite smaller figure, the Food and Drug Administration has specified a daily requirement of 600 I. U. for all persons irrespective of age. This figure is set as a minimum requirement and does not in any sense attempt to indicate the optimal amount of vitamin D necessary. Likewise, the Committee on Foods and Nutrition of the National Research Council has recommended a daily intake of 400 to 800 U.S.P. units for children under 1 year of age and for pregnant and lactating women. For older children and adults it is believed that optimal intake occurs almost spontaneously through exposure to ultraviolet radiation. When this does not occur, the daily intake through food sources and supplements should be maintained at around 600 U.S.P. units.

Absorption of vitamin D from the intestinal tract has long been considered to be affected by the conditions known to control the absorption of the other fat-soluble vitamins. In other words, the presence of bile and an intact mechanism for fat absorption have appeared to be important. The validity of these assumptions was proved by Forbes[3] who demonstrated the high postabsorptive concentration of chyle after the feeding of vitamin D concentrate to an infant. These levels rose ten-fold and forty-fold after four and six hours, respectively. It is probable, however, that the integrity of this mechanism is less important for vitamin D metabolism than for that of other fat-soluble substances because such large amounts of vitamin D are absorbed through the skin.

[3] Forbes, W. H.: J. Pediat., 25:191, 1944.

Breast-fed infants usually have less need for supplements than do artificially fed babies, particularly if the mother receives reasonable exposure to sunlight. For adults, it is widely believed that no dietary source of vitamin D is required; but, however this question is ultimately decided, it is obvious that few if any normal adults will obtain 600 I. U. daily through the diet alone. Indeed, the very lack of any really concentrated food source is in itself good evidence that under most circumstances vitamin D does not need to be made available by that route. Storage capacity in humans is not large and is confined chiefly to the liver.

The exact rôle of vitamin D in animal physiology, under more or less constant investigation for nearly two decades, remains obscure. Of the many specific functions of vitamin D that have been observed, several are of outstanding importance because of their relation to human pathology. The first of these is its effect in increasing the absorption of both calcium and phosphorus or in decreasing their reexcretion by the gut. The process takes place almost entirely in the small intestine. Uncertainty still exists as to which of these alternatives is more nearly correct, but the former seems to be supported by better evidence. In fact, there is some indication that phosphorus absorption is only secondarily affected. The mechanism of this action is not understood. Bile is known to be necessary for the transfer of vitamin D across the intestinal mucous membrane, as is also the case with the other fat-soluble vitamins. The specific effect of the vitamin in enhancing calcium ab-

sorption may be through some direct action on the mucosal cells, although parenterally administered vitamin D is as effective in this regard as oral preparations. The absorption of calcium is affected also by another factor which may be of considerable practical importance in the pathogenesis of rickets. This is phytic acid, or inositol hexaphosphoric acid, a constituent of many plants and cereal grains. This compound is believed either to precipitate calcium or to render it unabsorbable by converting it into an un-ionized complex. McCance and Widdowson[4] showed that the large amount of phytic acid (or phytate) in oats probably accounts for the rickets-producing effect of oat cereals which has been recognized for many years. Both the processing of oats and the manner of preparing the cereal for eating maintain the high content of phytate. These observations are not believed by McCance and Widdowson to be applicable to wheat cereals. Thus, the widespread occurrence of rickets and skeletal decalcification in some porridge-eating populations may be explained partially by this mechanism, which is related not only to the vitamin D supply but also to the dietary availability of calcium.

The second important effect of vitamin D is the maintaining of normal growth of the young. Available reports have concerned themselves entirely with the matter of skeletal growth, which is impaired in vitamin D deficiency. There is some evidence that excessive doses of concentrates (over 1,800

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[4] McCance, R. A., and Widdowson, E. M.: Nature, London, 153:650, 1944.

I. U. daily) will retard growth rather than increase it. The third and perhaps most important function is the least understood. It is known that vitamin D, after absorption from the intestine, exerts some sort of controlling action over the process of calcification at the epiphyses of growing bones. Bone formation at these sites takes place through the action of osteoblasts, which replace the degenerating cartilage cells. The enzyme phosphatase, the content of which is regularly elevated in rickets, plays some part in the scheme, probably by hydrolyzing the available blood phosphates to increase the local concentration of phosphate ions. In the absence of vitamin D, bone formation along the epiphyseal line does not proceed normally and the characteristic pathologic changes ensue. It is unfortunate that we do not understand this process more completely, but it has proved to be an extremely difficult problem to investigate. What light has been shed on the problem points toward a catalytic effect of some sort, entirely independent of the increased availability of bone salts and phosphatase, which is insured by the effect of vitamin D on the absorption occurring in the intestines. Whether or not the experimentally demonstrated effect of ascorbic acid on alkaline phosphatase is important in the rachitic process has not been determined, but there is a long-standing belief that the course of rickets is modified in some way by vitamin C.

Vitamin D deficiency leads to structural abnormalities of developing teeth of young animals, discussed in some detail later. After experimental bone fracture in

animals, it also causes delay in callus calcification and a significant decrease in bone strength of both fractured and intact bones. Observations of this type have not been made in human subjects, but there is no reason to believe that they do not apply in a general way in severe rickets in man.

The clinical picture of rickets is characterized by enlargement of the growing areas of the long bones, resulting in severe cases in definite deformities and associated with characteristic x-ray changes. The flaring of the epiphyses is most apparent in the wrists, knees and ankles. Figures 40, 41 and 42 show the bony changes in these areas. Equally as important as the flaring of the bone is the rough, irregular line of calcification at the end of the diaphysis, which under normal conditions is smooth and regular. Under proper, intensive therapy the irregularity of the rachitic line of calcification, within 10 days, shows areas of new calcium deposition which proceed gradually and steadily to a restoration of the normal structure. Total obliteration of these changes by means of therapy may require several months.

If such an area in a rachitic bone is examined histologically, the earliest demonstrable change is usually a failure of degeneration of the cartilage cells as they move from the epiphysis down toward the diaphysis. There is a coincidental lack of replacement by capillaries and new osteoblasts, which normally lead to deposition of new bone. Consequently the epiphyseal cartilage widens, and the line of calcification becomes irregular as a result of the rachitic proc-

Fig. 40.—Acute, untreated rickets. There is coarse trabecu-
lation of all bones. At end of diaphysis of radius and ulna, cal-
cification is rough and irregular. Distal epiphyses not visible
and end of bones not sharply defined. Same changes are
present in metacarpals. Age of patient, 6 months; gross
structural changes of chronic rickets therefore are not present.

Fig. 41.—Acute, healing rickets. Zone of new calcification at ends of both radius and ulna clearly defined. Same changes visible in distal ends of all metacarpals.

Fig. 42.—Acute rickets, healed. Healing is complete, with calcification of the entire zone at ends of all bones. Note sharp definition of these areas in contrast to that in Figure 40. Epiphyses still not visible because of youth of patient.

Fig. 43.—Low power photomicrograph of rachitic bone taken near epiphysis. Irregular line of calcification with bony trabeculae scattered among cartilage cells.

ess proceeding at varying rates of speed along the diaphyseal line. (Fig. 43.)

As these changes appear, general bone growth is retarded or ceases entirely. The bony changes in the ribs at the costochondral junction cause the formation of beading, the rachitic rosary and Harrison's groove. The weight-bearing bones, particularly the tibiae and femora, become bowed, with resultant diminution of stature and severe deformity. Craniotabes, or rachitic thinning of the skull, and potbelly are also characteristic features.

Characteristic laboratory findings during active rickets are first, a fall in the blood calcium level from the normal range of 9 to 11 mg. per cent to levels below the normal, the degree of change being roughly proportional to the severity of the condition. Calcium usually remains above 5 to 6 mg. per cent even in severe cases. The phosphorus, normally present in the blood in concentrations of 4.5 to 5 mg. per cent, also falls, but usually does not go below 2.5-3. Blood phosphatase, the best index of osteoblastic activity, is regularly elevated in rickets. The normal range for adults is 1.5-4 Bodansky units, and for children, 5-12 units per 100 cc. A moderate secondary anemia is usually present, and a generally poor nutritional status, often with other specific deficiency diseases, can frequently be recognized.

Therapy

Therapy for vitamin D deficiency is effective and simple in most cases. Cod liver oil U.S.P. is almost

universally available. It has been standardized at a minimum potency of 85 I. U. per Gm. Most of the commercial products, however, contain at least 100 units and some up to 400 units per Gm. A teaspoonful (about 4 Gm.) will therefore supply from 340 to 1,600 units. Viosterol U.S.P. must contain at least 10,000 I.U. per Gm. This potency is so high that it is usually prescribed by drops, each one containing 222 units. Unfortunately, the size of the drop will vary with the type of dropper, the temperature of the solution and various other factors, so that this method of administration, although probably satisfactory, is not accurate. Halibut liver oil is several times richer in vitamin D than cod liver oil. It is available on the commercial market with potency stated on the container. Percomorph oil is valuable because it is derived from fish liver oils which contain extremely high potencies of both vitamins A and D and diluted with oils of other species, so that the final concentration of vitamin D is not less than 10,000 units per Gm., or the same potency as viosterol.

In general, the chief advantage of the concentrated fish oils is their additional potency in vitamin A, which preparations of viosterol do not contain. In comparing the costs on the basis of units, cod liver oil will usually be found to be the cheapest, but owing to its relatively low potency, there are circumstances in therapeutics in which some more concentrated preparation is needed.

The minimum protective dose of vitamin D has already been stated as 600 units for all individuals

regardless of age or size. The source of this vitamin may be almost entirely from irradiation. It is probable that growing children and pregnant and lactating women should have from 800 to 1,200 units daily, but under most circumstances this is obtained chiefly from ultraviolet exposure. For prophylaxis for children, single large doses at intervals of three to six months have been advocated. Krestin[5] showed that this plan gave better protection than the daily administration of cod liver oil. Krestin used 300,000 I.U. in the form of 7.5 mg. of pure calciferol, administered orally in peanut oil. There was no evidence of toxicity, and the protection, followed for six months, was excellent during a period when there was no exposure to ultraviolet light. Although this method may have some practical advantages, it seems less physiologic than the daily use of small amounts of vitamin D. In the therapy of rickets already established, doses ranging from 1,200 to 60,000 units daily have been given. The former level obviously will act slowly but will lead to complete cure and probably represents a satisfactory therapeutic level. The Council on Foods and Nutrition of the American Medical Association recommends the use of 1,500-2,500 U.S.P. units daily for a period of months for the treatment of rachitic infants. Therapeutic doses may vary from 10,000 to 20,000 units daily. Certain cases of refractory rickets have been reported, response of which required up to 1,000,000 units. These instances are not common, and when they do occur careful differentiation must be made from

5 Krestin, D.: Brit. M. J., 1:78, 1945.

renal rickets, endogenous rickets and other obscure forms of deranged metabolism of calcium and phosphorus, conditions which can hardly be discussed in this volume.

A word should be added concerning the toxicity of vitamin D. Most of the early instances of toxic effects are now known to have been due to the administration of toxic sterols, associated with but not identical with vitamin D. The classic example of this was the case of vigantol, a German preparation which formerly contained toxisterol, a nonantirachitic decomposition product which may be produced by irradiation of ergosterol under certain conditions. The experimental literature relating to vitamin D in this connection is voluminous. Reed has summarized the factors influencing toxicity in humans as: (1) the dose per unit of body weight; (2) the duration of administration; (3) the composition of the diet in both minerals and organic matter; (4) the state of the alimentary tract; (5) individual susceptibility; (6) age; (7) preexisting pathology; (8) the vehicle in which the vitamin is administered; (9) the route of administration; (10) the functional state of the endocrine system; (11) the purity of the vitamin preparation; (12) the source of the vitamin, and (13) other factors as yet unrecognized. The incidence of this condition in humans fortunately is low, although it is probable that minor grades of toxicity are often overlooked. Danowski, Winkler and Peters[6] reported two

6 Danowski, T. S.; Winkler, A. W., and Peters, J. P.: Ann. Int. Med., 23:22, 1945.

cases in adults caused by the intake of large amounts of vitamin D in treatment of deforming arthritis. Renal damage and calcification of soft tissues were the chief clinical features, with abnormally high levels of serum calcium and phosphorus contents. Dosages in these cases ranged from 50,000 to 500,000 U.S.P. units daily for many months. Most of the toxic changes are reversible if they have not been present too long, but the recognition of such cases is a valuable warning against the use of vitamin preparations in dosages so far outside the physiologic range. There is no reason to believe that different forms of vitamin D vary in their toxic potentialities, and for most preparations the acute toxic dose appears to be in the region of 20,000 U.S.P. units per Kg. of body weight, or nearly 1,500,000 units daily for a man weighing 70 Kg. For the establishment of chronic toxic effects it is apparent that much smaller doses are open to criticism.

Use of Vitamin D in Other Conditions

True to the concepts of vitamin action as stated previously, vitamin D finds its best if not its sole field of usefulness in the treatment of specific deficiencies of this factor. In addition to rickets, *osteomalacia* is known to be a disease characterized by a lack of vitamin D. It occurs in adults and only under unusual conditions. The capacity of humans to provide their own antirachitic factor through irradiation makes it seem quite necessary that any serious grade of D deficiency must develop in individuals who not only need moderately large amounts of the vitamin, but

who in addition have practically no exposure to daylight except for that filtered through ordinary window glass. For these reasons, pregnancy will most often bring on the condition, which has many of the clinical features of juvenile rickets. Since the bones are not growing and the epiphyses are closed, softening takes place throughout the bone structure with resulting deformities. Treatment is effected through supplying the missing vitamin in appropriate dosage, as indicated earlier.

Arthritis.—Arthritis, of either the rheumatoid (atrophic) or the hypertrophic (osteo) type, has no element of deficiency of vitamin D involved in the etiology, so far as is known. The therapeutic effect of vitamin D is therefore entirely empiric and cannot be defined in terms of physiologic or pharmacologic principles. In actual practice it results from pushing the dose into the toxic range. Improvement in 74 per cent of a mixed group of arthritics was reported in one rather comprehensive study. Dosage was frequently around 300,000-400,000 units daily. The preparation most widely used in this work has been ertron, an electrically activated ergosterol dispensed in 50,000 unit capsules. No rational basis is known for the therapeutic effect and it therefore must be considered fortuitous and coincidental in a disease which is famous for its spontaneous exacerbations and remissions. The use of vitamin D preparations in arthritis not only cannot be recommended but must be discouraged as dangerous because of the hazards of toxicity. A great deal more study is needed but it is apparent that vitamin D

in this instance is being used as a pharmaceutical rather than as a vitamin. The American Committee for the Control of Rheumatism has stated its position thus: "At the present time therapy with large doses of vitamin D should be regarded as of doubtful, if any value."

Hypoparathyroidism.—Because of the capacity of vitamin D to raise blood calcium, its preparations have come into wide use in the treatment of hypoparathyroidism. This action and the benefit afforded in these cases are undeniable. A.T. 10, or dihydrotachysterol, a closely related sterol which has a marked blood calcium-raising action with little or no antirachitic potency, is another therapeutic agent which has proved to be highly effective in hypoparathyroidism. However, it appears to be no more effective than vitamin D concentrates. Indeed, vitamin D in doses of 10,000-200,000 U.S.P. units daily may be recommended as a highly satisfactory form of therapy. Dosage should be controlled by frequent observations of the blood calcium and phosphorus levels, with the object of maintaining the former at about 10 mg. per cent. In this way the therapeutic advantage of the drug may be obtained without any of the risks of intoxication, already outlined.

Other Diseases.—The use of vitamin D preparations for pollinosis, allergies of all types, acne vulgaris, psoriasis, hemorrhagic tendency in jaundice, eczema, cutaneous ulcers, trichinosis, lead poisoning, dental caries, prophylaxis against common colds and a score of other conditions can be dismissed with a few lines. Further experience may demonstrate a

valid rôle for vitamin D in some of these diseases, but for the most part its use has been empiric, the studies uncritical, and often the improvement attributed to vitamin D was due to some other nutritional factor.

VITAMIN E

The discovery of vitamin E dates back to 1922 when several investigators, particularly H. M. Evans, found that young rats reared on a diet consisting of purified protein, fat and carbohydrate, to which adequate salts and vitamins were added to assure normal growth, were unable to produce offspring. Fertility was restored by the addition of lettuce to the diet. These findings led to the belief that a "substance X," present in certain leafy vegetables and in some fats, was a necessary dietary component for the rat and that lack of this substance led to sterility.

An enormous amount of work since that time has revealed the essential nature of this factor, better known as vitamin E, and its importance for a variety of animal species including man. The investigations have elucidated certain details concerning the possible mode of action of the vitamin and have now yielded the compound in synthetic pure form. With the pure synthetic material available, clinical studies are being carried on in many different places, and it is hoped that the true rôle of this vitamin in human nutrition will be clarified in the near future.

Chemical characterization of vitamin E was accomplished in 1938, and synthesis followed almost immediately. Credit for this achievement goes to a num-

ber of investigators, particularly to P. Karrer, who not only is responsible for the present accepted formula for this compound but actually synthesized it before the structure was known.

Wheat germ oil proved to be the best natural source of vitamin E, and from it were isolated several active compounds known under the generic classification of
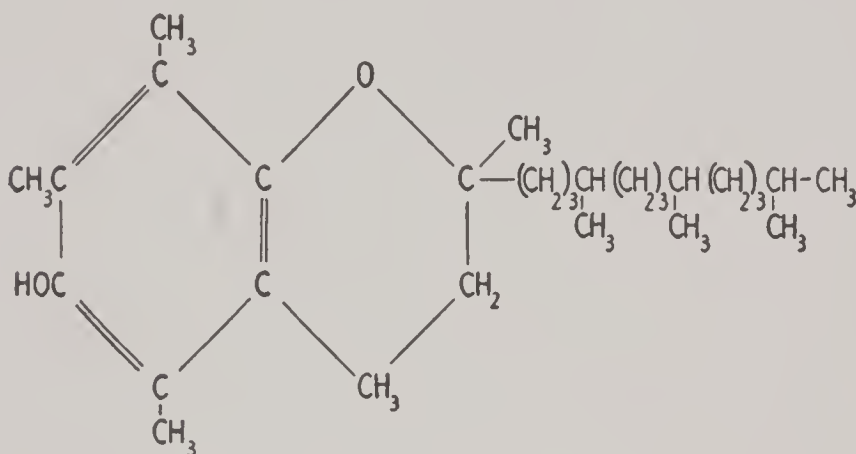
Fig. 44.—Vitamin E (alpha tocopherol).

tocopherols. The most potent of these is alpha tocopherol, which now stands as the official chemical designation for vitamin E. It is more probable, however, that vitamin E will eventually be found to consist of a complex of factors, the combined effect of which will constitute the nutritive action of the naturally occurring substance.

From the structural formula, the fat solubility of the vitamin would be anticipated. Its most outstanding chemical characteristic is its strong reducing or antioxidant power, on which its biologic action probably depends to a great extent. It is interesting that

the long side chain attached to the benzene ring is phytol, an alcohol which forms a part of the molecule of the important plant pigment, chlorophyll.

There are no available lists of potencies of various sources, but the vitamin is present in greatest concentration in green leafy vegetables and in vegetable oils. The highest concentration occurs in wheat germ, and the oil from this source provides the basis for commercial preparations of the vitamin. Accurate, dependable assays of food sources for alpha tocopherol have not been made, so it is not possible to list these values. In addition, no agreement has been reached concerning a unit for standardization of wheat germ oil. There exist at present two units, designated as the Evans-Burr unit and the Pacini-Linn unit, neither one of which can be expressed in weight of alpha tocopherol. This is due probably to the quite recent availability of the pure preparation for use as a standard of comparison as well as to the lack of a sharp end-point in animal assay methods. Finally, no standard preparation has been set up thus far against which unknown materials can be assayed, although an approach to the solution of this problem has been made. The median fertility dose in female rats as tested independently by 13 laboratories varied from 0.5 to 1.71 mg. of synthetic racemic tocopheryl acetate. This great variation provides strong evidence of the need of an international standard.

Development of a suitable chemical method for estimation of the tocopherols in tissues and body fluids by application of the iron-bipyridine color reaction prom-

ises to add significant information concerning the participation of vitamin E in metabolic processes.[1] The method has been adapted by Minot,[2] for estimation of tocopherols in blood serum. By means of this technic normal serum levels have been reported as 0.19 and 0.22 mg. per cent for men and women, respectively. In dystrophic children values of 0.74-1.28 mg. per cent were obtained, levels which did not differ from those of a control group of normal children.[3]

The exact mode of action of the vitamin E complex, the tocopherols, is not positively known, but numerous suggestions have been offered. The existence of these substances was first discovered, as has been mentioned, through their indispensability in the maintenance of normal fertility in rats. Rats fed diets which are free from vitamin E or diets which have been treated with ferric chloride to destroy this factor are able to initiate pregnancy in normal fashion. Early in gestation, however, the fetuses die and are resorbed. Degenerative changes in the corpora lutea of deficient rats have been observed as early as the sixteenth day of pregnancy.[4] These changes are reversible in the female, since administration of adequate doses of potent material will permit subsequent pregnancies to go to term. In the male, deficiency leads to an irreversible degeneration of the seminal epithe-

1 Hines, L. R., and Mattil, H. A.: J. Biol. Chem., 149:549, 1943.

2 Minot, A. S.: J. Lab. & Clin. Med., 29:772, 1944.

3 Minot, A. S., and Frank, H. E.: Am. J. Dis. Child., 67:371, 1944.

4 Einarson, L., and Ringsted, A.: *Effect of Chronic Vitamin E Deficiency on the Nervous System and Skeletal Musculature in Adult Rats* (New York: Oxford University Press, 1938).

lium of the testis, resulting in permanent sterility. The mechanism of these changes is most puzzling, for the deficient animals regularly show histologic changes in the anterior pituitary gland of a type suggesting castration. Whether these are primary or secondary is uncertain, but at least it has not been possible to maintain the integrity of the testis or of the products of conception by any type of pituitary gonadotropic preparation thus far tried. Effects of vitamin E deficiency on other endocrine organs are strikingly similar to those produced by hypophysectomy, namely, adrenal atrophy and thymus hypertrophy, as well as changes in the gonads in both sexes. The thyroid increases in size up to 100 per cent. Placental transfer of vitamin E is nil in the rat and mammary transfer is exceedingly small.

A totally different type of pathology has also been noted in experimental animals as a result of deficiency of the tocopherol complex. Einarson and Ringsted have summarized in a complete review the changes produced by this condition in the nervous system and skeletal musculature of adult rats. These changes are degenerative, progressive, the result of long-continued deficiency disease, and eventually lead to death of the animal. In the spinal cord the proximal parts of the posterior nerve roots are first affected, followed in order by the anterior horn cells, the anterior roots and the pyramidal tracts. Muscular atrophy and degeneration accompany the degeneration of the nervous system. The symptoms and the pathologic lesions are strongly suggestive of certain human diseases, particularly tabes dorsalis, progres-

sive spinal muscular atrophy and combined system disease of pernicious anemia.

Still another type of muscle degeneration has been studied extensively by Spencer, Morgulis,[5] Pappenheimer and Goettsch and others. This type is produced only in rabbits and guinea-pigs by means of a diet in which the food has been treated with ferric chloride to destroy the vitamin E. In these animals, myopathic lesions develop in contrast to the myelopathic lesions in the former group. The muscle degeneration is of particular interest because histologically it resembles the pathologic picture of human progressive muscular dystrophy. Recent work has indicated, however, that lack of more than one factor is not involved in the production of this experimental disease and that it is cured by alpha tocopherol alone. Much remains to be clarified concerning both of these experimental diseases, but they are of more than passing interest because of their possible bearing on problems in human pathology.

Interest in the relationship of the tocopherols to human diseases of muscle was reawakened by the report of Milhorat and Bartels[6] that a combination of inositol and alpha tocopherol reduced creatine excretion in patients with muscle dystrophy. By chemical treatment these investigators were able to produce a condensation product of unknown composition which they believed would be 2,500 times as effective in this

5 Morgulis, S.: *Nutritional Muscle Dystrophy;* in Terroine, E. F. (ed.): Nutrition. XVI (Paris: J. Hermann, 1938).

6 Milhorat, A. T., and Bartels, W. E.: Science, 101:93, 1945.

specific function as that produced by simple ethylene dichloride extraction of wheat germ oil. They obtained this effect, measured chemically, in a series of patients, but clinical improvement did not run parallel. The meaning of these observations in terms of clinical medicine cannot be evaluated until the work has been widely extended.

Following the excellent demonstration by the Danish investigators of the myelopathic lesions of vitamin E deficiency, it was inevitable that the attention of clinicians should be attracted to the possibility that a nutritional etiology might be involved in some human diseases of the nervous and muscular systems. Additional impetus was provided by the synthesis and availability for clinical trial of pure alpha tocopherol. A number of reports have appeared in the medical literature dealing with the treatment of a variety of pathologic conditions with the synthetic drug. Chief among these conditions have been amyotrophic lateral sclerosis, progressive muscular atrophy and tabes dorsalis. Promising results were reported in each of these as well as in myasthenia gravis, myotonia atrophica and spinal cord degeneration from pernicious anemia. However, this whole matter has been subjected to more critical evaluation, and the results are uniformly disappointing. Careful investigation has been handicapped by the lack of any quantitative method for the estimation of tocopherol in body fluids. Use of the chemical method for clinical studies may clarify these confused relationships. Nevertheless, on the basis of extensive, long-continued clinical trials one seems jus-

tified in expressing a strong doubt that a simple lack of tocopherol plays any part whatever in the pathogenesis of these conditions of such varied etiology and, further, that the administration of that compound affects the course of any of these diseases. It should be pointed out, however, that the evidence is equally strong that vitamin E deficiency is responsible for the appearance of both muscle and nerve lesions in certain experimental animals.

Even the most widely accepted application of vitamin E to therapy has yet to be justified. Despite numerous reports of the efficacy of this vitamin in the treatment of sterility, threatened abortion and inadequate lactation, sufficient evidence is lacking to demonstrate that a deficiency of this factor plays any part in human reproduction. In many of the cases studied, progesterone was also given, and in many others progesterone alone was used. Results in general appear to be promising, but a great deal more critical work is obviously required. Wheat germ oil concentrate is the preparation of vitamin E usually employed, and dosages have ranged from 1 to 4 drachms daily by mouth. Mention should be made of the interesting reports of Shute, who finds that the blood serum of aborting women resembles that of E-deficient rats in its resistance to tryptic proteolysis. Restoration to normal in both instances followed administration of wheat germ oil. This work has not been repeated or confirmed by other investigators and therefore cannot be accepted. The manner of action of tocopherol in reproductive proc-

esses remains obscure. The suggestion has been made, on rather inadequate evidence, that alpha tocopherol is active in maintaining reproductive functions, while beta tocopherol functions in preventing muscular and nervous degeneration. There is no evidence to decide this point.

From the chemical point of view, a logical suggestion has been put forth by Hickman. He has observed the protective antioxidant action which alpha tocopherol exerts on the integrity of vitamin A and other carotenoids. He feels that this may represent one of the chief, if not the most important, function of this substance in biologic systems. Additional weight has been provided for this point of view by an extensive series of investigations which has corroborated the protective action of the tocopherols on fats, especially those with a high content of unsaturated fatty acids known to be highly susceptible to oxidation. The body fat of rats raised on a vitamin E-deficient diet is abnormally susceptible to oxidation.[7] Also, the development of vitamin E deficiency is strikingly influenced by the character of fat in the diet. Unsaturated fats hasten the development of deficiency symptoms, whereas saturated and rancid fats have no effect, a fact which suggests that unsaturated fats, which need protection from oxidation, are responsible for the effect.[8] The importance of tocopherol in reproduction in animals may possibly be explained by this same protective action for sex hormones, nutritional factors or

[7] Barnes, R. H.; Lundberg, W. O.; Hanson, H. T., and Burr, G. O.: J. Biol. Chem., 149:313, 1943.

[8] Dam, H.: Proc. Soc. Exper. Biol. & Med., 52:285, 1943.

enzyme system components which are not identified. Indeed, the protection against oxidation seems to be the most probable common denominator to explain a series of diversified and apparently unrelated functions.

Attention has been drawn to another claim made for vitamin E by Shute and his co-workers, who described a dramatic response of hypertension and hypertensive cardiovascular disease on administration of this vitamin. Information regarding these claims has been available chiefly through the public press, and the claims are regarded with skepticism by investigators and students in the field. Such effects must be thoroughly substantiated and controlled by many groups of observers before they can be accepted.

Of equal interest, and somewhat more rational, is the observation by the same investigators[9] that the thrombocytopenia and increased capillary permeability of experimental animals given large doses of estrogens can be returned rapidly to normal by the administration of 200-400 mg. doses of vitamin E daily. The effects appeared by the seventh to eighth day. Equally dramatic results were achieved in clinical purpuras of varied etiology, including idiopathic thrombocytopenic purpura and hypertensive cardiovascular disease. These results also must be checked and verified, although it is known that a possible experimental basis for these findings is reasonably well established.

It is clear that our knowledge of vitamin E is woefully incomplete. We know nothing of the human re-

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9 Skelton, F.; Shute, E.; Skinner, H. G., and Waud, R. A.: Science, 103:762, 1946.

quirements and too little about its biologic function.
Many of the animal experiments and nearly all of the
clinical studies are poorly controlled and uncritical and
have not yielded clearcut information such as we pos-
sess regarding many other nutritional factors. That it
has an important biologic rôle is an almost inescapable
conclusion. The widespread changes in the endocrine,
nervous and muscular systems resulting from its defi-
ciency would lead one to believe that many interesting
functional relationships will be brought to light as the
place of this vitamin in animal physiology is elucidated,
but there is no convincing evidence that any human
disease or any disturbance of child-bearing or locomo-
tion in human beings is due to deficiency of vitamin E
or is alleviated by treatment with it.

VITAMIN K

The earliest recorded observations which led to the discovery of vitamin K were those of Henrik Dam who, in 1929, while investigating some details concerning the metabolism of cholesterol, discovered incidentally that his experimental chickens regularly had subcutaneous and intramuscular hemorrhages. Clotting of the blood was greatly delayed unless certain additions were made to the diet. Further exploration of this problem during the next few years established numerous sources for this antihemorrhagic factor, later named vitamin K, among which was fish meal which had been allowed to putrefy. The potency of this material was lost by ether extraction. The mechanism of the defect in blood coagulation was identified in 1935 as a deficiency in prothrombin which was promptly restored to normal by the administration of an adequate supply of vitamin K. Clinical application of this experimental work followed almost immediately after laboratory methods had been devised by which the prothrombin content of human blood could be estimated with reasonable accuracy. A fitting climax to the researches which had gone before was provided by the work of Doisy and his group who, in 1939, isolated and chemically identified two active antihemorrhagic compounds,

thereby paving the way for the synthesis which fol-
lowed almost immediately.

The antihemorrhagic vitamin acting through the
mechanism of a prothrombin deficiency has now been
shown to be a property of each one of a group of
compounds having the general structure shown in
Figure 45. Actual analysis of the active components
from naturally occurring sources has provided the
structural formulas for several of this group. The
first of these, designated as vitamin
K_1, has substituted a phytyl group for
the R in the general formula which
immediately relates it to chlorophyll
of plants and to vitamin E. The sec-
ond member of the series, vitamin K_2,
which has been derived from fish meal,
contains a slightly different group on
R′. Other interesting members of
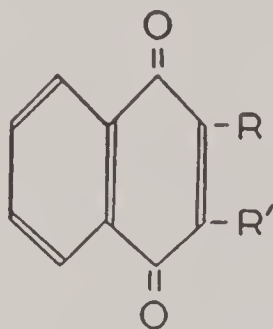
Fig. 45.—Vitamin K.

the series are phthiocol, which is produced by the
human tubercle bacillus, and 2-methyl-1, 4-naphtho-
quinone, one of the most active antihemorrhagic sub-
stances isolated thus far. The latter compound is
used as a basis for standardization of vitamin
K activity, 1 unit representing the antihemorrhagic
activity of 1 µg. of 2-methyl-1, 4-naphthoquinone.[1]
Although most of the compounds in this group are in-
soluble or sparingly soluble in water, several have been
prepared which are water-soluble and therefore suit-
able for intravenous administration. Prominent among

[1] The Council on Pharmacy and Chemistry of the American Medical
Association has authorized "menadione" as the nonproprietary name for
this substance.

this latter group are two new members, 2-methyl-4 amino-1 naphthol and 2-methyl-1, 4-naphthohydroquinone disuccinate, both of which are commercially available for parenteral (including intravenous) injection. 2-methyl-1, 4-naphthoquinone is sparingly soluble in either warm saline or water and may also be given by injection. Another water-solube form, designated vitamin K_3 has been described by Russian investigators. It is derived from the corn stigma and is alleged, without confirmation, to possess antihemorrhagic activity superior to that of other known factors.

From the chemical standpoint it is now recognized that only compounds of the 1, 4-naphthoquinone series have significant antihemorrhagic potency, but it is interesting to note that some other substances, convertible during metabolism to the active type of structure, also have good potency. There is some evidence to suggest that vitamin K activity is dependent on the reversible oxidation-reduction properties possessed by these compounds, a fact which may help to explain the extremely minute amounts required for physiologic effects. Claims have also been made that the various vitamin K compounds are degraded physiologically to either salicylic or phthalic acid, to which the antihemorrhagic action is really due. This theory of the mechanism has not been supported by further work; however, it is well recognized that salicylates, including aspirin, have an anti-vitamin K action which lowers blood prothrombin. The effect can be combated by the use of vitamin K in such a ratio that 1 mg. of 2-methyl-1, 4-naphthoquinone will counteract about 1

Gm. of acetyl salicylate. This action of salicylates is probably of questionable practical importance except possibly in instances of excessive use of those drugs.[2]

There is much interest in the relationship between the prothrombin-reducing action of dicoumarol and the opposing effect of vitamin K. In rats, vitamin K administered either before, during or 12 hours after the giving of dicoumarol will prevent the hemorrhagic effect of the latter.[3] Identical results in man have been reported by Shapiro and his associates,[4] although the dosage of vitamin K must be relatively large.

The chief sources of vitamin K are the leafy portions of many young, growing plants. Alfalfa, wheat, oats and grass have been found to be particularly rich in this factor. It is formed in the chloroplasts along with chlorophyll. Leaves grown in the dark and so containing no chlorophyll, as well as plants like the mushroom, also contain no vitamin K. On the other hand, spruce and pine which are able to produce chlorophyll in the dark are said to be able to form vitamin K in the dark. In addition, vitamin K activity appears to be conferred on certain substances by bacterial action. Thus, tuna fish meal is inactive unless allowed to putrefy, after which its potency is marked. Probably under normal conditions bacterial action plays an important part in supplying the human requirement for this vitamin. Indeed, it has not yet

[2] Meyer, O. O., and H. B.: Proc. Soc. Exper. Biol. & Med., 53:234, 1943.
[3] Overman, R. S.; Field, B. J.; Baumann, C. A., and Link, K. P.: J. Nutrition, 23:589, 1942.
[4] Shapiro, S.; Redish, M. H., and Campbell, H. A.: Proc. Soc. Exper. Biol. & Med., 53:251, 1943.

been satisfactorily proved that humans require this factor preformed in the diet, although it has been clearly demonstrated for some experimental animals. On the other hand, it has been satisfactorily established that these naphthoquinones are as necessary in the human as in other animal species for the production of prothrombin. The possibility must still be considered that all of the human needs can be supplied through the action of the normal intestinal flora on various of the foodstuffs or through independent synthesis from constituent building materials. This would mean that the chemical precursors of vitamin K or the necessary bacterial nutrients must be present in the diet, the release of the potent compounds then being a function of bacterial action. It is therefore evident that vitamin K deficiency in humans is unlikely to result from dietary inadequacy alone, unassociated with other abnormalities. This point of view has received support from a series of investigations in which sulfonamides were used to reduce bacterial flora in experimental animals.[5] In this work prothrombin levels were conspicuously reduced by administration of the various sulfonamides by both the oral and the parenteral route. The potency of the various drugs assumes the same order of sequence in their effect on prothrombin levels as they have in their bacteriostatic effect on coliform organisms. The concentrations of the drugs in the cecal contents rise regardless of the

[5] Black, S.; Overman, R. S.; Elvehjem, C. A., and Link, K. P.: J. Biol. Chem., 145:137, 1942; Kornberg, A.; Daft, F. S., and Sebrell, W. H.: J. Biol. Chem., 155:193, 1944.

method of administration. Thus, the significance of bacterial synthesis in vitamin K requirements is unmistakable, and the development of deficiency states in man must be interpreted in the light of these findings.

Because of the uncertainty about human requirements, it is unnecessary to list the vitamin K potency of various foods. Such assays are not available in terms of weight units. Bio-assays have been conducted on a variety of naturally occurring materials but the units in which these data are expressed are confusing. Five independent units were created by various investigators for measurement of this potency, the units of Dam, Dann, Ansbacher, Thayer and Almquist, but they have been superseded by standardization on the basis of potency of pure synthetic 2-methyl-1, 4 naphthoquinone. Colorimetric methods for measurement of vitamin K content of biologic materials are being studied and when available may greatly simplify clinical work. At present, all vitamin K potencies and deficiencies are measured in terms of prothrombin levels.

There are six recognized causes of prothrombin deficiency in man, all of which can be detected by laboratory tests and all of which are characterized by a tendency to abnormal bleeding. In the order of their importance, they are:

1. Absence of bile in the intestinal tract. Since vitamin K is a fat-soluble substance, the presence of bile is necessary to transport it across the intestinal mucosa for absorption into the portal blood. Thus, in obstructive jaundice of all types, prothrombin defi-

ciency is a potential hazard for this reason alone. Administration by mouth of adequate sources of the vitamin must obviously be associated with simultaneous administration of bile salts to permit satisfactory absorption.

2.   Extensive liver damage. Under these conditions the necessary materials from which prothrombin is synthesized are available, but the organ in which synthesis takes place is unable quantitatively to perform its function.

3.   Defective absorption from the intestine for other reasons. It has been reported that in certain types of chronic diarrhea the intestinal rate may be so rapid that absorption is impaired. In sprue this deficiency may likewise develop since intestinal absorption for all food factors is defective. Subnormal blood prothrombin levels have been reported under many such circumstances. Probably such a mechanism is not common, but its existence does seem reasonable from physiologic considerations alone.

4.   Inadequate intake of vitamin K or its precursors in the diet. Although reports in the literature which bear on this point are not numerous, it is probable that this is important and it appears certain that a dietary source of some indispensable factors will be found necessary. The only alternative to this would be the demonstration that intestinal bacteria can build the vitamin K molecule out of almost elemental constituents, a possibility which seems highly improbable.

5. Administration of dicoumarol, salicylates or other drugs which depress blood prothrombin levels through

an effect on liver synthesis. The effect is reversible and
n the case of dicoumarol, at least, is produced delib-
erately to prevent thrombosis.

6. Long-continued use of sulfonamide drugs. De-
pression of blood prothrombin levels by this means
depends on inhibition by the drug of biosynthesis of
vitamin K by normal intestinal flora.

Mention should also be made of the rare condition
known as idiopathic hypoprothrombinemia, a familial
disease of unknown etiology associated with a bleeding
tendency and not attended by liver damage.

All forms of hypoprothrombinemia except that due
to the second cause respond to vitamin K in proper
dosage. Emphasis should be placed on the second cause
since it constitutes the chief, if not the only, obstacle to
successful vitamin K therapy. Assuming that bile is
being produced and gaining access to the intestinal
tract, prothrombin deficiency may still develop under
conditions of adequate supply and absorption of vita-
min K if the liver is so damaged that it is unable to
produce sufficient prothrombin to maintain a normal
level in the circulating blood. Under these circum-
stances it is obvious that no amount of vitamin K
therapy will be of any value, since the liver is incapable
of response. For cases of this sort, the only possible
effective treatment must consist of supply from ex-
ternal sources of preformed prothrombin in quantities
sufficient to restore the blood coagulation mechanism
to normal. At present such a method is not available,
except through the inadequate expedient of blood trans-
fusion. This will provide insignificant amounts of

prothrombin which may improve blood coagulation for a short time, but no permanent gain is achieved through this procedure and duration of the effect is often too brief even to allow surgery to be performed. If and when pure preparations of prothrombin become available on a large scale, the outlook in cases of this type may improve considerably. In terms of specific pathologic states, liver damage of this order of magnitude may be anticipated in cirrhosis of all types, hepatitis, acute and subacute yellow atrophy and extensive destruction of hepatic tissue by neoplasm or inflammation. Under these conditions, measurement of the response of blood prothrombin to adequate vitamin K therapy constitutes a dependable test of liver function.

Widespread interest, especially among obstetricians and pediatricians, has been created by studies on the mechanism of the physiologic bleeding tendency in new-born infants. Because it is associated with a lowered prothrombin content of blood, its cause has been thought to be a deficiency of vitamin K, due to inadequate transmission of that substance across the placenta. The subsequent lack of adequate food and the absence of proper intestinal flora delays the establishment of adequate fetal stores of the vitamin and resulting production of prothrombin. There is no reason to believe that the capacity of the fetal liver to form prothrombin is impaired, since administration of sufficient amounts of vitamin K to the mother before delivery or to the infant post partum effectively restores prothrombin to normal. Opinion on the practical value of these measures derived from actual

clinical experience is divided. Several excellent studies have appeared based on large series of cases, all of which have led to the conclusion that fetal mortality and fetal hemorrhage may be significantly reduced by administration of vitamin K. A smaller number of observers have been unable to detect any appreciable therapeutic advantage from the use of vitamin K. The large number of complicating factors such as trauma, infection and other deficiencies admittedly make the control of such investigations difficult, and conclusions must be based on large statistical studies. With few exceptions the accumulated evidence indicates highly satisfactory results from administration of vitamin K to the mother before or during labor or to the infant immediately after delivery. Since the administration of vitamin K preparations has no adverse effects and since the preponderance of evidence favors its use, it appears justifiable to endorse this therapy which has become widely and firmly established in clinical practice.

Little has been added to our knowledge of the coagulation of blood since Howell proposed his theory more than 25 years ago. The present concept of that process is best illustrated by the diagram shown in
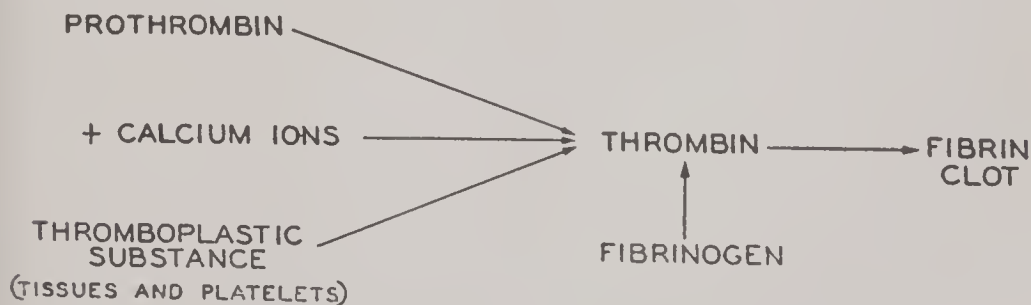
Fig. 46.—Diagram of blood coagulation.

Figure 46. Both prothrombin and fibrinogen are known to be formed largely, if not exclusively, by the liver, so that hepatic insufficiency may impair blood coagulation at either stage. The exact rôle of the naphthoquinone structure of vitamin K compounds is not understood, but it is apparently necessary for the formation of prothrombin, probably not as a constituent part of the molecule itself.

The chemical and physiologic behavior of prothrombin is gradually being elucidated, and this added knowledge promises to contribute significantly to our understanding of the clotting process. Prothrombin is a protein, probably with a fairly small molecular weight since it moves in an electrical field with albumin. Its formation is undoubtedly an enzymatic process, as may also be its conversion into thrombin. Vitamin K does not appear to be incorporated into the protein molecule, since after proteolytic digestion the residue has no vitamin K potency. The measurement of prothrombin content of venous blood theoretically may be accomplished by supplying in adequate amounts all of the necessary constituents for the reaction excepting prothrombin. The time required for clotting is, then, a quantitative measure of the latter, although a deficiency of fibrinogen will not be detected by this technic. From a practical standpoint several methods have been devised, but considerable difficulty has been encountered in arriving at a satisfactory agreement among the various investigators interested in this problem. The methods of Quick and of Warner, Brinkhous and Smith and various modifications of both

all give reliable results after sufficient experience in their use has been obtained.

Therapy of Vitamin K Deficiency

The early clinical work with vitamin K was carried out through the use of preparations from putrefied fish meal and from extracts of alfalfa. Evaluation of potencies was difficult, so that early therapeutic trials were not on a quantitative basis. The earliest commercial preparation of this substance, called cerophyl, was a mixture of dried, powdered young cereal grain plants (oats and wheat). Another commercial concentrate, named klotogen, was prepared from alfalfa. In the past few years, the pure synthetic naphthoquinones have become commercially available so that therapy has been simplified and standardized.

Oral administration of vitamin K concentrate is usually most satisfactory when bile salts are also given, since by far the largest group of patients requiring this therapy are those with liver and biliary tract disease, usually with jaundice.

There are a great many preparations of vitamin K available commercially, derived from both natural and synthetic sources. Because of the chaotic situation relative to the various units of potency, there has been considerable confusion in standardization of dosages. However, using synthetic 2-methyl-1, 4-naphthoquinone as a reference standard, some uniformity may be attained, for the average therapeutic dose of that compound is 1 mg. daily. If given by mouth it should be accompanied, in subjects with obstructive jaundice,

by administration of bile salts, usually in the form of ox bile in amounts up to 3 or 4 Gm. daily. Amounts in excess of this may cause nausea and vomiting and, in addition, are not necessary for adequate absorption of the vitamin. Inadequate doses of either the vitamin or the bile salts may cause failure of therapy.

When given by the intravenous route, one of the water-soluble forms must obviously be used, and again the dosage should be 1 mg. daily. Use of bile salts under these conditions is unnecessary. Since no toxic manifestations from these preparations have been reported, there is no particular contraindication to slightly larger doses, up to 2 or 3 mg. daily, but their use is certainly not necessary.

Dosage of concentrates varies widely because of the lack of uniformity in their preparation. 2-Methyl-1, 4-naphthoquinone has been assayed at from 20,000 to 40,000 Dam units per mg., which represents also the average therapeutic dose. Generally speaking, the equivalence of other units has been calculated by the manufacturers, and the recommended doses for each preparation should be followed. Many of these are in tablet form and some are in sterile oily solution. The latter type may be administered by subcutaneous or intramuscular injection, although this is rarely necessary.

Response to adequate therapy appears within a few hours; it is not uncommon to observe a complete return of prothrombin time from exceedingly low levels to normal within 18 hours.

In treatment of the hemorrhagic tendency of the

new-born, it is common practice to give to the mother 1 mg. by mouth two or three times weekly during the final weeks of pregnancy. Administration by injection is not indicated except for some special reasons, such as when the first opportunity for therapy presents itself at the onset of labor and the time factor in absorption from the intestinal tract assumes greater importance. Vitamin K may be administered also to the new-born infant immediately after delivery. It has been shown that 10 μg. is sufficient to bring the prothrombin level to normal for several days, but there is no contraindication to the use of 0.1 mg.

Failure of response when adequate therapy has been given by mouth or parenterally usually means severe liver damage, unless it can be shown to be due to some other interfering factor. This rule applies especially when the vitamin is used intravenously. Since there is normally a substantial but thus far un-measured storage of antihemorrhagic factor in the body, the failure of response or a lack of maintenance of improvement after therapy may be regarded as a fairly reliable quantitative measure of liver function, since it has been found to parallel results of other of the more reliable liver function tests. As already stated, in the absence of satisfactory increase in blood prothrombin in response to the aforementioned therapy, there is no method known at present for overcoming the obstacle of hepatic insufficiency. This measure offers little practical benefit, since most sur-geons will justifiably refuse to operate when the risk of serious hemorrhage is so great.

The entire history of vitamin K from its discovery through subsequent developments up to the present has been so dramatic and rapid that clinicians have actually been hard pressed to keep apace with the fundamental progress made by the biochemists. Although there remain many aspects of this subject for future exploration, there has already accrued to the medical profession the virtual elimination of one of the most perplexing problems in surgery, namely, the hazard of hemorrhage during or following operative procedures on jaundiced patients with disease of the liver or biliary tract.

MINERALS

It is well known to the medical profession and the laity alike that the human body needs a constant intake of numerous mineral elements in order that deficiencies may not develop. Most important among these are iron, calcium, phosphorus and iodine. Of less practical importance are the trace elements, copper, zinc, cobalt, manganese and magnesium. Certain other elements are so universally and abundantly present in all foods that their adequate intake is assured. Examples of this type are sulfur, sodium and potassium.

Sodium

Intake of sodium is largely in the form of common salt, which is a constituent of meats and is added in the preparation and serving of most vegetable foods. Actual intake of salt may vary from about 2 to as much as 30 Gm. per day depending on taste. Equilibrium is usually maintained by the ready renal excretion of any excess of either sodium or chloride. A further significant source of sodium is a variety of salts of organic acids in vegetables and fruits. These compounds are oxidized during metabolism, leaving a residue of sodium bicarbonate, the alkaline reserve of body fluids. Diets high in animal or cereal foods

tend to be low in sodium bicarbonate formation, but diets high in vegetables and fruit provide a balance by furnishing the needed sodium. This is likewise true of other metals such as potassium and magnesium, and calcium which contribute "alkaline ash."

A characteristic of the meat and cereal group of foods is their capacity to provide significant amounts of phosphorus and sulfur which are excreted as phosphate and sulfate. These salts carry with them in renal excretion a certain amount of the metals, chiefly sodium, but they are only incompletely neutralized in the urine, which is therefore kept at an acid reaction. This is the normal state of bladder urine. Except for brief periods of special therapy it is not wise to make any attempt to feed sufficient salts of sodium to render the urine alkaline. There is no risk in normal health that the excretion of sulfate and phosphate will deplete the body of sodium, for the kidneys are able to form ample amounts of ammonia as a substitute for the various metals before the serum concentration of sodium becomes subnormal. On the other hand, with a high intake of hypertonic saline, as in the imbibition of sea water, the kidney is confronted with the physiologic impossibility of excreting large amounts of sodium chloride and other mineral elements in the presence of a constantly diminishing content of water with which to perform the excretion. Each addition of the hypertonic solution augments the mineral excess until physiologic dehydration supervenes which is incompatible with life.

Another source of loss of sodium is the sweat, which

contains salt in concentrations somewhat less than that of serum. Copious perspiration may remove more salt in a day than ordinarily passes out through the kidneys. This phenomenon is the basis for the now widely recognized need for extra use of dietary salt or for drinking salted water in hot weather during vigorous exercise or with fevers. The salt may be provided in any one of several obvious ways, but the concentration introduced into the stomach should not be more than 1 per cent or nausea may be the result.

Another side of this problem has been provided by a series of human experiments which have contributed somewhat to our knowledge of acclimatization to tropical heat. One such representative study[1] showed that acclimatized men could maintain physical fitness under humid tropical conditions on a salt intake as low as 5 Gm. per day owing to the physiologic adjustment of a salt concentration in sweat that falls sharply in a manner paralleling the conservation of salt by the kidney. The volume of sweat decreased simultaneously. Under conditions of these experiments, men doing hard physical labor should be able to maintain normal health on average salt intakes of 10-15 Gm. daily. These observations do not necessarily apply when hard physical labor ceases, under the same living conditions. A later communication by the same investigators[2] provides evidence that this effect is integrated through the adrenal cortex, for desoxycorticosterone was found to

[1] Conn, J. W., and Johnston, M. W.: J. Clin. Investigation, 23:933, 1944.

[2] Conn, J. W.; Johnston, M. W., and Louis, L. H.: Proc. Am. Soc. Clin. Investigation (1946), p. 14.

produce a sharper fall in sodium chloride concentration of sweat.

Since salt is quantitatively the most important mineral in the serum and interstitial fluids, removal of that element will lower the osmotic pressure of these solutions. Because osmotic equilibrium must be maintained, removal of water, replacement of salt, or both, may occur. The water is eliminated by excretion through lungs and skin, and any remaining excess passes out in the urine. The volume of urine per day is a dependable guide to the excess of water above physiologic needs. The kidneys excrete almost no water unless there is an excess after the processes of respiration and perspiration have occurred. For minimal tasks of excretion, it is safe to instruct most individuals that the amount of water needed is at least that daily total which will allow excretion of 1 L. of urine. Smaller volumes tend to impose greater chemical tasks on the excretory apparatus and may lead to slight retention of waste products.

The interstitial fluids and lymph serve as a reservoir of water and salt, among other materials, and act as buffers in case of loss or abnormal accumulation of salt or water. As a consequence, the changes in concentration of circulating blood are very slight, for the volume of interstitial fluids exceeds that of the serum. The buffering tends also to protect the tissue cells from exposure to marked changes in concentration of salts and water with attendant disturbance of function.

Sodium chloride serves a poorly understood function

in the pigmentation of the skin. Spoor and Ralli[3] showed that the feeding of hypertonic saline to rats, with resulting dehydration, caused changes in the melanin content of skin similar to the effects of a diet deficient in the "filtrate factor" which produces nutritional achromotrichia. Thus, an error in salt metabolism, related to impaired adrenal cortical function, may be the clue to the complex phenomenon of pigmentation in Addison's disease.

These complicated mechanisms require little conscious attention from the healthy human or from the physician. Thirst usually serves to induce adequate water intake. Normal salt ingestion ordinarily is sufficient for usual needs since the interstitial fluids buffer slight changes over short periods of time. For persons with obvious sweating, prolonged vomiting (chloride loss) or diarrhea (sodium loss), extra salt should be provided. There is little danger of excess, for renal excretion is efficient. Of course, excesses may be dangerous if renal activity is reduced by nephritis or by circulatory impairment secondary to congestive heart failure. On the other hand, circulatory failure due to reduced blood pressure associated with lowered blood volume may be more quickly reestablished by introduction of salt and water as physiologic saline than in any other way.

Potassium

In nearly all instances in which an abnormality in the metabolic behavior of potassium has been recog-

[3] Spoor, H. J., and Ralli, E. P.: Endocrinology, 35:325, 1944.

nized, the underlying cause has been endocrine rather than nutritional. In view of the abundance of potassium in Nature, it is difficult to imagine a potassium deficiency occurring except under experimental conditions. Estimates of the potassium content of the human body vary between 0.11 and 0.35 per cent, so that the body of a 70 Kg. man probably contains about 175 Gm. of elemental potassium, concentrated in body cells with only small amounts in body fluids. Intake and excretion roughly balance each other and amount to about 3.5 Gm. daily. Most excretion takes place through the kidney. Normal blood levels range from 4 to 5 milliequivalents per liter. Regulation of potassium distribution and balance is largely under control of the adrenal cortex, a detailed discussion of which is outside the scope of this volume.

Potassium has been related to a great number of functions, but the details of the mechanisms are poorly understood. It is necessary for growth; in experimental animals a deficient intake of potassium results in impaired growth. It is important in carbohydrate metabolism. In Addison's disease with low blood sugar levels, the serum potassium content is high, and in uncontrolled diabetes mellitus both sugar and potassium values are usually high. Injection of insulin causes a simultaneous fall in both blood sugar and blood potassium levels. Excitability of both nerve and muscle is correlated with potassium metabolism, and in synaptic transmission of the nerve impulse this element seems to possess an acetylcholine-like function.

The participation in some mysterious way of potassium in the rare and interesting disease known as "periodic muscular paralysis" deserves mention. This familial condition transmitted as a sex-linked recessive character consists of periodic attacks of complete or partial muscular paralysis without loss of consciousness. During such attacks the blood potassium level falls sharply without comparable excretion, indicating in all probability that the loss of muscle function is correlated with a high intracellular potassium level. Restoration of the normal balance with extracellular fluids quickly relieves the attack. This can be done by administration of potassium, by exercise or by production of anoxia of large groups of muscles. The etiology is unknown and the pathologic physiology also is poorly understood, but the knowledge we do possess concerning this disease serves to emphasize the vital part played by potassium in the intracellular chemistry of muscle.

A wide variety of foods is rich in potassium. It is a normal constituent of both plant and animal cells, so that both vegetable and meat diets contain abundant amounts. It is because of its wide natural distribution that no naturally occurring deficiency of potassium has ever been recognized. Low intakes formerly were advocated in Addison's disease, but with the steady improvement in adrenal cortical extracts and synthetic materials available for treatment, this therapeutic expedient has been abandoned. Fenn[4] summarized our present knowledge of potassium in an excellent review.

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[4] Fenn, W. O.: Physiol. Rev., 20:377, 1940.

Iron

The average adult human has a total of about 4.3 Gm. iron; 2.7 Gm. is present in the circulation, most of it as hemoglobin, 0.3 Gm. as functioning tissue iron, and about 1.3 Gm. as storage iron for use under emergency conditions such as hemorrhage. The circulating iron exists in three forms: (1) hemoglobin iron present in the red cells; (2) "easily split off iron," in combination with some unidentified products of hemoglobin breakdown; (3) serum iron, part of a complex radical in the ferric state and probably in combination with serum globulin. This last mentioned fraction appears to be the main mechanism of iron transport.

The body holds on with such tenacity to its iron stores under normal circumstances of health that there is practically no loss through the common pathways of excretion such as the bile, urine, feces and perspiration. Any normal losses that do occur certainly do not exceed a few micrograms daily. This conservation of iron is effected mainly through the excretion by the liver of bile pigments, biliverdin and bilirubin which are iron-free, the iron having been efficiently removed during the processes of hemoglobin degradation, thereby allowing that element to be stored for use over and over again.

From a practical standpoint this means that iron deficiency must be produced either by blood loss, by some set of metabolic conditions which involve an increased demand for iron, such as normal growth in childhood and adolescence or pregnancy and lacta-

tion, or by chronic infection which affects absorption of iron, increases the demand for it and diverts ingested or injected iron in an abnormal manner. In a study of the anemia of chronic infection, Cartwright and his associates[5] showed that it has certain characteristics consisting of normocytic cells, markedly depressed serum iron content, elevated serum copper values, increased red cell protoporphyrin and coproporphyrinuria. From these data it appears that iron gaining access to the body, by whatever route, is diverted to the tissues in such a manner as to make it unavailable for hemoglobin synthesis. As a consequence, absorption from the intestine is possibly increased, but the unavailability of absorbed iron for metabolism causes the accumulation of copper and protoporphyrin because they cannot be used for hemoglobin production. Correction of the defect by administration of iron is not possible because the function of iron in relation to infection, unknown at present, has a higher priority than the synthesis of hemoglobin.

Absorption of iron from the intestinal tract is a much more complicated process than was formerly realized. Using radioactive iron, Moore and his coworkers[6] showed that iron-deficient humans absorb 1½-15 times more ferrous than ferric iron, confirming older findings by other technics. Since the level of body iron under physiologic conditions remains quite constant, with negligible excretion, as shown by McCance

[5] Cartwright, G. E.; Lauritsen, M. A.; Humphreys, S.; Jones, P. J.; Merrill, I. M., and Wintrobe, M. M.: Science, 103:72, 1946.
[6] Moore, C. V.; Dubach, R.; Minnich, V., and Roberts, H. K.: J. Clin. Investigation, 23:755, 1944.

and Widdowson[7] some years ago, it is clear that a regulatory function is assumed by the intestinal epithelium. Hahn and his associates[8] demonstrated rapid saturation of the mucosa within a few hours after administration of an oral dose, so that further absorption of iron was prevented for several days. Iron deficiency resulted in an increase of five to 15 times the rate of iron absorption over that of healthy individuals. Grannick[9] extended knowledge of this process by showing a marked increase in "ferritin" concentration in the guinea-pig intestinal tract after the feeding of iron. Ferritin is a combination of a protein, apoferritin, with ferric hydroxide, and it is believed to be in equilibrium in the mucosal cell with ferrous iron, which, in turn, is in equilibrium with serum ferrous iron. After saturation, following the administration of iron, absorption is stopped until desaturation of ferrous iron occurs, as it passes into the serum and thence to other tissues for storage or use. From this evidence it is not difficult to understand the well recognized clinical evidence for poor iron absorption in all conditions showing a normal serum iron level. The one noteworthy exception is the anemia of chronic infection, described above, in which low serum iron content is not attended by satisfactory hemoglobin regeneration.

With an increased need for iron from whatever cause, the iron requirement may rise to such levels that

[7] McCance, R. A., and Widdowson, E. M.: Biochem. J., 31:2029, 1937.

[8] Hahn, P. F.; Bale, W. F.; Ross, J. F.; Balfour, W. M., and Whipple, G. H.: J. Exper. Med., 78:169, 1943.

[9] Grannick, S.: Science, 103:107, 1946.

the diet alone will not fill the need and supplements are required. The optimal daily intake of iron has been estimated at 15 mg. for individuals of all ages, but the greater part of this obviously will not be utilized by healthy adults.

In normal young women the menstrual blood loss represents true iron excretion which must be balanced by a correspondingly augmented intake. The magnitude of the loss, however, is not great. Some recent balance measurements have shown satisfactory iron storage in normally menstruating women when the intake varies between 7 and 10 mg. per day. It is likely that the actual iron requirements, even under these conditions, is considerably less than 7 mg. Indeed, estimate of the minimal daily requirements for humans under normal metabolic conditions has undergone a steady revision downward, although the Food and Nutrition Board of the National Research Council still recommends 12 mg. daily for men and women, 15 mg. daily during pregnancy and lactation and 15 mg. daily for adolescent boys and girls.

Hypochromic anemia, the classic example of iron deficiency, may be subdivided into several types, and in each the true need for added iron intake is apparent. In this disease the cells are small and poorly filled with hemoglobin but of normal shape and structure. Hemoglobin values are depressed more than the number of red cells, and the color index is therefore low. Serum iron values may fall almost to zero. The abnormality lies in the production of hemoglobin rather than in the production of red cells, and since

iron is the limiting factor, the administration of this element in adequate amounts results in a rapid and often dramatic response. Indeed it is sometimes possible to measure the increase in circulating hemoglobin as a quantitative recovery of iron given. Approximately 25 mg. iron is necessary to produce a rise of 1 per cent of hemoglobin in an adult under these conditions.

The idiopathic form of this disease occurs more commonly in females, in whom the regular blood loss from menstruation plays an important part. Many patients have had one or more pregnancies, and often other sources of significant blood loss can be identified. Such factors all combined in the presence of a deficient intake may eventually cause a depletion of reserve iron stores with resulting anemia of this type.

In young girls just past the menarche, the factor of growth, which further augments the need for iron, is added to all of the other factors previously mentioned. Chlorosis, the iron deficiency anemia of young girls, results from these circumstances, but fortunately the incidence of this condition has been greatly reduced by the widespread understanding of its etiology.

Dietary iron is chiefly in the form of hemoglobin and other complex molecules. For its absorption from the gastro-intestinal tract, normal gastric acidity provides a definite advantage but does not seem to be absolutely necessary. Of the inorganic iron salts, the simpler ones appear to be most effectively absorbed even in the absence of hydrochloric acid. In addition, ferrous salts are more efficient than are ferric salts.

The presence of large amounts of phosphate in the diet, or the administration of phosphates as medication may cut down iron absorption from the intestine significantly because of the formation of insoluble iron phosphate.

Ferrous sulfate is one of the best forms in which to administer iron supplements, with ferrous carbonate (Blaud's pills) and ferric ammonium citrate occupying slightly inferior positions. Maximum dosages usually used are 2 Gm. (30 gr.), 6 Gm. (90 gr.) and 6 Gm., respectively. It is evident that these dosages supply much more iron than can be used effectively by the body. Although better results usually have been obtained with the higher doses, it is quite possible that this advantage may be related to the copper and cobalt supplied by these large supplements rather than to an effect of the excess of iron itself. Further clinical investigation of this matter is needed. The most important iron-containing foods are:

Asparagus	Heart	Spinach
Beans, dried	Peas	Beets
Beet greens	Lettuce	Beans, green
Bran	Oysters	Fish
Chard	Whole wheat	Potatoes
Dandelion greens	Watercress	Prunes
Egg yolk	Oatmeal	Brussels sprouts
Liver	Soy beans	Broccoli
Kidney	Apricots	
Beef	Tomatoes	

Copper

The best available evidence at present indicates that copper is necessary to humans in minute amounts for processes involved in hemoglobin production, although the element is not actually present in the

hemoglobin molecule. Copper is also known to be a constituent of several important enzymes in which it exists in complex organic combination.

Experimental animals placed on iron-deficient diets, such as milk alone, develop a hypochromic type of anemia which is not benefited by the administration of iron but improves rapidly if copper also is added to the diet. This work suggested that a similar mechanism might operate in some types of human anemia. Unfortunately, there has been relatively little clinical work to explore this possibility, but several instances of successful use of copper have been reported which seem to indicate that the functional importance of that element in animals applies also to humans. Special emphasis should be laid on the effectiveness of copper in treating the anemias of childhood. The efficacy of liver extracts of various types in the treatment of secondary anemia may be found to be attributable to the minute amounts of copper which they contain rather than to any more complex substance.

The average human requirement for this element is unsettled, but it probably does not exceed 2 mg. The mean daily intake has been set at approximately this same amount, and the optimum has been estimated as 100 μg. per Kg. body weight for children and about 60 μg. per Kg. for adults. Excretion occurs mainly by way of the bowel, and varies from 0.2 to 1 mg. daily. Blood contains 50-150 μg. per cent of copper. The best food sources are egg yolk, liver, bran, lobster, shrimp, oatmeal, leafy and leguminous vegetables and cereal grains.

Calcium

Calcium is the most abundant mineral element in the animal body. A man weighing 70 Kg. (155 lb.) has been estimated to contain about 1,200 Gm. of elemental calcium. The function of this substance in animal economy is primarily to build bone, but it serves also to maintain an important osmotic balance in the blood and tissues on which the integrity of muscular contraction and other processes depends. The importance of calcium as a component of body fluids may perhaps best be appreciated by recalling that the parathyroid glands act as a special homeostatic mechanism for regulating the balance between intake and output, the tissue distribution and the ionization of calcium in the body.

Absorption of calcium from the gastro-intestinal tract is influenced by many factors. An acid medium favors ionization of calcium salts and increases their solubility. Large amounts of phosphate, oxalate, phytate or fat in the diet tend to reduce absorption because of formation of insoluble calcium salts. Diarrhea with a rapid intestinal rate reduces absorption, which partially explains the chronic calcium deficiency in sprue and related disorders. Finally, vitamins C and D both facilitate the utilization of calcium through mechanisms that are not understood.

Needs of healthy adults have been estimated at between 0.6 and 0.7 Gm. daily, in which the demand is entirely for replacement of loss. In growing children, however, when new bone is being formed, the requirement is certainly not less than 1 Gm. daily and may be

as high as 1.5 Gm. In pregnant and lactating women the need for calcium is as great as that in children. In fact, if the milk supply is abundant, lactation may call for even a larger intake of this element if the body stores are to be preserved. It must be borne in mind that even under the best conditions only about 20 per cent of dietary calcium is absorbed.

In all considerations of the metabolism of calcium it is especially important to remember that enormous, easily mobilized stores of this element exist in the bones and that consequently it is impossible to have an acute calcium deficiency unless other pathology exists as the underlying cause. Inadequate intake over long periods results only in a substantial loss from the bones which is gradually replaced if and when the dietary source is restored to normal. Hyperparathyroidism represents the most severe drain on calcium reserves, since excretion is constantly above normal and disproportionate to intake for long periods. Even in this condition, however, a surprising length of time is required before bony defects can be demonstrated by x-ray. For these reasons it is possible for an otherwise healthy adult to survive relatively protracted periods of inadequate calcium intake without appreciable difficulty. The blood level is constantly maintained, and the teeth and supporting portions of the bones are preserved at the expense of the reserve supply in cancellous bone. It is important to remember that in osteoporosis of various types, a deficient intake of calcium is almost certainly not involved in pathogenesis. Endocrine factors are of much greater im-

portance. Likewise, in the rampant dental caries often seen in pregnant women and frequently attributed to calcium deficiency, other metabolic phenomena are actually the cause. Despite the fact that a healthy woman has a tremendous store of calcium, great enough to build a fetal skeleton, good management of pregnancy insures a calcium intake by the mother of at least 1.5 Gm. daily so that these stores may be preserved.

Of all food materials, dairy products are probably the best sources of both calcium and phosphorus, and these elements are present in the optimal ratio of approximately 1.2:1. A quart of milk contains about 1.15 Gm. calcium and will therefore supply the needs of even growing children and lactating women. Most cheeses contain about 1 per cent of calcium and are likewise excellent sources. Other important foods are:

Buttermilk	Soybean flour	Broccoli
Egg yolk	Wheat bran	Cauliflower
Clams	Dried figs	Oatmeal
Sardines	Green olives	Cocoa
Shrimp	Turnip greens	Maple syrup
Almonds	Peas	Molasses
Hazelnuts	Dried beans	

The therapeutic administration of additional calcium is most effective in the form of the lactate, gluconate or chloride. Although they will all admirably serve the purpose, the last mentioned is perhaps the most efficient of the three because of its high calcium content and because of its acid hydrolysis which aids in absorption. Solutions up to 25 per cent may be given; the astringent taste is best concealed by the use of any strongly flavored vehicle. Total dosage for any form of calcium should provide 2-4 Gm. daily.

There is rarely any necessity for giving calcium salts parenterally except for their pharmacologic action.

Phosphorus

Phosphorus is so abundantly present in a variety of foods that it requires less attention than calcium. Most proteins contain a generous supply of this element, but dairy products of all types are the best sources, as in the case of calcium. An adult male needs about 0.9 Gm. and a child about 1.3 Gm. phosphorus daily. Since 1 qt. milk contains approximately 0.9 Gm., it will go far toward supplying this entire need. Other important sources are:

Eggs	Peas	Pineapple
Liver	Beans	Corn
Whole wheat	Carrots	Cucumber
Oatmeal	Asparagus	Peanuts
Bran	Cauliflower	

It is rarely necessary to give supplements of phosphorus in addition to the food supply, since, as in the case of calcium, there exists a large store in the bones, because of which relatively long periods of inadequate intake may be disregarded so far as practical measures are concerned.

There are many vital functions of phosphorus in connection with bone, muscle, nerve tissue and specific organs which cannot be further elaborated on in the present discussion. In addition to a rôle in bone structure equal in importance to that of calcium, it is also involved in the enzyme reactions by which carbohydrate is burned.

Iodine

The importance of iodine in metabolism is chiefly, if not solely, related to thyroid function. Since this element is a constituent of the thyroglobulin molecule, a deficiency of thyroid secretion will occur in the absence of an adequate intake of the former. There are certain areas throughout the world where the soil and water appear to be lacking in iodine, the most important one in the United States being in the region of the Great Lakes. In such areas, the use of iodized salt has been found to be a valuable prophylactic measure against the widespread occurrence of colloid goiter. The minimum daily human requirement of iodine is thought to be only a fraction of a milligram, and the richest food sources are sea foods of all types. Important plant sources include barley, green beans, bran, broccoli, butter, carrots, cherries, corn, loganberries, oats and spinach, but it must be emphasized that the iodine content of vegetables depends on the soil in which they are grown. For this reason, foodstuffs coming from endemic goiter areas are likely to be deficient in iodine. Under such circumstances the use of commercial iodized salt, containing from 0.01 to 0.015 per cent iodine, is probably the best solution to the problem of iodine supply.

The practice of using iodized salt has been objected to on the basis of its taste and color. In addition, analyses of commercial salts have revealed iodine losses up to 63 per cent owing to the oxidation of the iodide with subsequent sublimation of the elemental iodine. The addition of an antoxidant has been found

to prevent this loss and to render the salt colorless, odorless and free from objectionable taste. As this method of preparation of salt becomes more common, it is hoped that the use of the iodized product will become universally accepted throughout the endemic goiter areas.

Manganese

This element is usually present in relatively large amounts in normal diets (4 mg. daily), but the human requirement is unknown. It is excreted in the urine in amounts of 10 μg. or less per L., suggesting that the greater part of the dietary supply is not absorbed from the intestine. In experimental animals manganese functions as activator to several enzymes, and a lack of it has been shown to cause sterility, failure to suckle the young and a disease in fowls called slipped tendon disease. Its rôle in humans has not been investigated. Chief dietary sources are vegetables and cereal grains.

Magnesium, cobalt, tin and lead require only passing mention. They are of no practical significance at present because their function is unknown. They are present in animal tissues and may be necessary for humans in trace amounts.

PROTEIN

The Need

The importance of proteins in human nutrition can hardly be overemphasized. Occupying as the proteins do a unique position in the constitution of living matter, the preservation of an adequate supply to the tissues becomes a matter of the utmost importance. Protein food may be regarded as useful in metabolism in four different ways:

1. It is necessary for the construction of new tissue and for the repair of wear-and-tear processes.

2. It is necessary for the synthesis of many enzymes, antibodies, hormones and pigments, which themselves are proteins.

3. It may be used as fuel for energy purposes under conditions of stress, although it is not burned preferentially.

4. It may be stored as fat after chemical transformation, probably through carbohydrate, when great excesses of food are available.

In addition to these vital uses, protein in our diets has other functions. It contributes much to the physical consistency and flavor of food. Protein food stimulates the oxidative process as a whole to the extent of 5-10 per cent in the day's total, when com-

pared with metabolism on a protein-free diet. This is the specific dynamic effect, caused by most foods but more intense from protein. During the first hour after a liberal intake of protein the increase in heat production may be as much as 50 per cent above the previous level. The consequent warming of the body is a valuable mechanism for comfort and sense of well-being in cold climates. The products of digestion of proteins stimulate the flow of secretions from the gastric and intestinal mucosa, thereby facilitating the digestion of the other foods present.

From these considerations it becomes evident that protein is needed throughout life. The greatest amounts are used during the periods of most rapid and extensive growth. After adult proportions have been attained, significant amounts of tissue are formed following such events as infections, with destruction of leukocytes and other tissues, and trauma, with the granulation process of repair and hemorrhage which necessitates the replacement of cell and plasma proteins. Pregnancy and lactation impose special demands for protein food. Even in healthy adults, without any of these complications, there is the slow and relatively small loss of epidermal protein in hair removal and the unavoidable attrition of the skin. Except for growth and reproductive functions these protein needs are seldom great enough to require conscious attention, simply because the amounts demanded are smaller than the margin between the total requirement of the body and the conventional protein intake. The usual diets of people who are not near the margin of subsistence

contain more protein than is necessary for safety. During good health the adult probably needs only a small amount of protein daily to replace the sum of the losses mentioned and those caused by the destruction or excretion of certain enzymes, hormones, hemoglobin and mucus.

It is now generally known that proteins are compounds of carbon, hydrogen, oxygen, nitrogen, sulfur and phosphorus and that the constituent building blocks, the amino-acids, may be linked together into enormous aggregates with total molecular weights of many millions. The chemical structures of such compounds are obviously very complex, but they constitute the structural basis for living matter. The extremely complicated variety of proteins can be surmised from several general concepts. All proteins are very large molecules, the molecular weights of which are 100-1,000 times the weight of glucose. These large protein molecules are made up of smaller constituent molecules, the amino-acids, of which there are more than 20 distinct types in animal tissues. In even the simplest proteins there are probably more than 100 such amino-acid units united to form one protein molecule. Not every protein contains each constituent. Further variety is provided by the proportions of the various amino-acids used by the body in building the different proteins, even when the constituent amino-acids are the same. Another distinguishing feature is conferred by the manner in which any two amino-acids may be linked chemically to each other. Some proteins are further characterized by combination with phosphorus, sulfur,

sugar, lipids or complex pigment molecules. With such numerous possibilities for variation in composition and structure it is not surprising that there are wide divergences in solubility, viscosity, coagulability and digestibility of the many recognized proteins.

As one consequence of this tremendous variety of protein molecules, differentiation of cells, tissues, individuals and species became possible. The distinguishing features of these biologic classifications are related to the nature of the proteins in the cells involved. Each type of cell has its characteristic protein, and even the differences between two individuals of the same species must be associated with variety in kind and amount of proteins.

Such facts need not suggest that the individuals of any species must secure their protein from the bodies of other animals of the same species. The dietary proteins not only are built up of amino-acids but during digestion are again resolved into solutions of the same amino-acids. From the residues of digested protein, whether beef, pork, milk, egg or wheat, the human body builds up tissue which is characteristically human. It is obvious that the amino-acids liberated during digestion must include all those typical of human proteins, i.e., all the natural amino-acids known in proteins. But neither the manner of the original linkage nor the proportion of the amino-acids in the food proteins decides what the final human protein is to be like. This is determined by the human tissues, probably by properties of self-reproducing protein molecules in the chromosomes. It will be apparent that often the food

protein may proffer the tissues excesses of certain amino-acids and deficiencies of others. The excesses are oxidized as sources of fuel, by methods which resemble the utilization of carbohydrates and fats.

All amino-acids, of which 22 are recognized, are not equally indispensable in metabolic processes. The brilliant investigations of Rose and his co-workers have clarified our knowledge of the amino-acids to such an extent that it is possible to maintain adequate protein nutrition in human subjects for extended periods without administration of food by mouth. Rose's classification of the amino-acids is shown in Table 12.

TABLE 12.—FINAL CLASSIFICATION OF AMINO-ACIDS WITH RESPECT TO THEIR GROWTH EFFECTS*

INDISPENSABLE	DISPENSABLE
Lysine	Glycine
Tryptophan	Alanine
Histidine	Serine
Phenylalanine	Norleucine
Leucine	Aspartic acid
Isoleucine	Glutamic acid
Threonine	Hydroxyglutamic acid
Methionine	Proline
Valine	Hydroxyproline
Arginine†	Citrulline
	Tyrosine
	Cystine

* From W. C. Rose: The Nutritive Significance of the Amino Acids, Physiol. Rev., 18:109-136, January, 1938.

† Arginine can be synthesized by the animal organism, but not rapidly enough to meet the demands of normal growth.

NOTE.—Of the 10 amino-acids known to be essential for growth in the rat, at least eight have been shown to be necessary also for humans.

It is evident from this biologic division that if any one of the essential list is excluded from the diet, or if it is present in less than adequate amount, no excess of all the others can compensate and protein equilibrium will be disturbed, with catabolism exceeding anabolism, nitrogen excretion exceeding intake and a negative

nitrogen balance ensuing. In addition, there is evidence to suggest that the limiting factor in the utilization of even biologically complete proteins is their content of the essential amino-acids. Emerson and Binkley[1] reported that the daily intravenous administration of a mixture of the 10 essential amino-acids resulted in a marked improvement in utilization of food protein taken orally by human patients with marked protein deficiency. This suggests that the utilization of protein food, regardless of its high intrinsic biologic value, may be significantly improved by supplementing its content of essential amino-acids. Experimental deficiencies of single amino-acids have been studied in animals and to a limited extent in man, but such conditions are not known to occur naturally in humans. General protein starvation in humans, on the other hand, is well known and has been studied intensively both experimentally and under conditions of famine resulting from the war. Indeed, the maintenance of an adequate daily intake of protein of satisfactory quality may be considered the greatest single problem in the rehabilitation and survival of hundreds of millions of starving people in many parts of the world.

In studies of the constituent proteins of human tissues, attention has been focused primarily on those of blood, antibodies, hormones and enzymes, supplemented by investigations of the effects of protein starvation and the amino-acid constitution of many important food proteins. Separation of blood proteins into two

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[1] Emerson, K., and Binkley, O. F.: J. Clin. Investigation, 25:184, 1946.

main fractions, albumins and globulins, by chemical
methods is widely known, but the further subdivision
into alpha, beta and gamma globulins and fibrinogen
by the electrophoretic method of Tiselius and by ultra-
centrifugation is less familiar. By the latter methods,
the analysis of human blood plasma[2] has revealed the
following composition:

Albumin	55%
Alpha globulin	13
Beta globulin	14
Gamma globulin	11
Fibrinogen	7

The original rough chemical separation was made on
the basis of water-solubility and molecular weight.
Serum albumin is a relatively small molecule with a
molecular weight of about 70,000 and high solubility
in water. This protein contributes about 80 per cent of
the total osmotic pressure of plasma. Since each gram
binds approximately 18 cc. of water within the vascular
system, albumin is responsible to a large extent for the
maintenance of circulating blood volume. This fraction
is known to be produced almost entirely by the liver,
so that hepatic damage is usually indicated by lowered
levels of plasma albumin.

The combined globulin fractions constitute a much
larger group of protein molecules, with molecular
weights ranging from 150,000 to 500,000 and much
lower solubility in water but good solubility in salt
solutions. Included in the globulin fractions are many
substances of the greatest importance: for example,

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[2] Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., and Arm-
strong, S. H.: J. Clin. Investigation, 23:417, 1944.

the immune bodies and complement, the isohemagglutinins, various hormones, enzymes such as alkaline phosphatase, the blood-clotting components, hypertensinogen and the immune bodies. These fractions are made by the reticulo-endothelial system located chiefly in the liver, spleen, bone marrow and lung and to an important degree also by the lymphoid tissue throughout the body. The osmotic effect of the globulins is much less than that of albumin, but their vital rôles in physiologic processes and in defense against injury are so evident that the ultimate practical value to medicine and surgery that we may hope to derive from large-scale preparation of these pure constituents needs no further comment.

Progress in the chemistry of immunity has added a vital new chapter to our knowledge of the proteins. The subject was well reviewed by Cannon.[3] The evidence of correlation between the antibody content of blood and the gamma globulin fraction becomes increasingly convincing. In protein depletion from either experimental or natural causes, reduction of resistance to bacterial infection parallels the decline in blood globulins. This relationship finds natural expression in the enormous increase of epidemic bacterial disease that usually accompanies famine conditions, and it adds significant weight to the time-honored belief that malnutrition predisposes to infection. The clinical implications of these basic principles are far-reaching and tend to emphasize to practicing physicians everywhere

[3] Cannon, P. R.; in Anson, M. L., and Edsall, J. T. (eds.): *Advances in Protein Chemistry* (New York: Academic Press, 1944).

the gains that may be anticipated from a close super-
vision of nutrition in both preventive and therapeutic
medicine.

Concepts of intermediary protein metabolism have
undergone striking changes during recent years. The
experimental work of Whipple and his associates,[4] and
the isotope studies of Schoenheimer[5] and many others
have contributed significantly to this change. Whipple's
group is responsible for the concept of a "dynamic
equilibrium" in the body between the so-called fixed
tissue proteins and the more labile blood proteins. The
circulating proteins must be considered the peripheral
phase, most readily observed and measured, of the gen-
eral balance between supply and demand for protein
throughout the body. Although accurate measurement
of plasma protein fractions may be expected to reflect
the rough over-all status of this equilibrium, it is in-
creasingly apparent from balance studies that protein
deficiency may exist without significant alterations in
the blood picture. For this reason it is not justifiable
to assume adequate protein nutrition on the basis of
normal plasma findings, since changes in these meas-
urements may lag considerably behind significant dis-
turbances in nitrogen balance. Studies by tracer tech-
nics, using marked or labeled proteins and amino-acids,
demonstrate a constant interchange of protein con-
stituents between all types of body proteins, with a high

[4] Whipple, G. H., and Madden, S. C.: Medicine, 23:515, 1944; Fink,
R. M.; Ennis, T.; Kamball, C. P.; Silberstein, H. E.; Bale, W. F.;
Madden, S. C., and Whipple, G. H.: J. Exper. Med., 80:455, 1944.

[5] Schoenheimer, R.: *The Dynamic State of Body Constituents* (Cam-
bridge, Mass.: Harvard University Press, 1942).

rate of turnover of these materials between tissues and organs. Thus there is much greater instability in the constitution of even the fixed tissues than was realized before these methods of investigation had clarified the metabolic picture. Further expansion of these researches may be expected to provide knowledge of specific biochemical processes that can be turned to the practical management of clinical problems.

Requirements

There is an old belief that the minimal protein requirement for a healthy adult is about 0.5 Gm. per Kg. of body weight daily, although a suboptimal level might possibly be maintained by a somewhat lower intake. This figure, however, depends on several other known factors, the most important of which are the coincident intake of carbohydrate and the quality of protein consumed. Since carbohydrate is the fuel of choice, it has an important protein-sparing action by eliminating the necessity for utilization of protein for energy purposes.

Most well nourished adults eat 70-110 Gm. of protein daily (calculated as dry weight), a significant part of which, according to classic teaching, should come from animal sources. Recent studies, however, have demonstrated the completeness of some vegetable proteins in the nutrition of rats and dogs without supplements from animal sources. In man, similar experiments using very small proportions of animal proteins have been conducted. It is well known that certain vegetable sources are nutritionally satisfactory, and there is considerable evidence to suggest that humans may be ade-

quately nourished for prolonged periods from exclusively vegetable sources. Table 13 gives the essential amino-acid constitution of some important food proteins, based on recent analyses. Physicians must possess dependable information concerning the protein requirements in all types of physiologic and pathologic conditions which they are called upon to manage.

Protein requirements may be altered by a wide variety of physiologic and pathologic conditions, most of which are attended by an increase of the need. These include exposure to excessively hot and cold climates, growth, pregnancy, trauma and debilitating diseases.

Climate.—There is no evidence that either increased demand for body heat or increased expenditure of physical energy causes a rise in protein requirement provided adequate fuel foods are available. In the absence of necessary amounts of carbohydrate and fat, however, the conversion of protein for energy purposes must be proportionately increased. An interesting recent study has demonstrated the superiority of a high fat intake over that of both carbohydrate and protein for maintaining optimal energy balance during exposure to extreme cold. The effect is augmented by frequent feedings instead of the usual three meals daily. The specific dynamic action of protein causes a substantial rise in heat production during the immediate postprandial period and is attended by a sense of warmth which may be subjectively highly desirable in cold climates and equally undesirable in the tropics. In neither circumstance is there any known alteration in protein requirement as estimated by objective criteria.

TABLE 13.—Amino-Acid Composition of Proteins*

	Egg White	Egg Yolk	Whole Egg	Casein	Whole Milk	Human Milk	Beef Muscle	Chicken Muscle	Fish Muscle	Liver	Wheat Flour	Corn	Rice	Leafy Vegetables	Peanut Meal	Brewers' Yeast	Soy Bean Meal	Whole Wheat
Arginine........	5.8	8.2	7.0	4.2	4.3	6.8	7.7	7.1	7.4	6.6	3.9	4.8	7.2	7.0	9.9	5.3	5.8	5.0
Histidine........	2.2	1.4	2.4	2.5	2.6	2.8	2.9	2.3	2.4	3.1	2.2	2.5	1.5	2.1	2.1	3.0	2.3	1.7
Lysine........	6.5	5.5	7.2	7.9	7.5	7.2	8.1	8.4	9.0	6.7	1.9	2.0	3.2	5.7	3.0	7.4	5.4	3.0
Tyrosine........	5.4	5.8	4.3	6.9	5.5	5.1	3.4	4.3	4.4	4.6	3.8	5.6	5.6	5.4	4.4	3.5	4.1	3.0
Tryptophan........	1.7	1.7	1.5	1.4	1.6	1.5-3.1	1.3	1.2	1.3	1.8	1.3	0.8	1.3	1.9	1.0	1.5	1.2	1.0
Phenylalanine......	5.5	5.7	5.9	5.2	5.3	5.9	4.9	4.6	4.5	6.1	5.5	5.0	6.7	4.5	5.4	4.6	5.7	5.6
Cystine........	2.6	2.3	2.4	0.3	1.0	2.3-3.9	1.3	1.3	1.2	1.3	1.9	1.5	1.4	2.0	1.6	0.9	0.9	1.1
Methionine........	4.4	...	4.9	3.5	3.3	2.5	3.3	3.2	3.5	3.2	3.0	...	3.4	2.3	0.9	2.8	2.0	2.5
Threonine........	4.3	...	4.9	4.1	4.6	4.5	4.6	4.7	4.5	4.8	2.7	3.7	4.1	4.1	1.5	5.3	4.0	3.3
Leucine........	...	...	9.2	9.9	11.3	10.1	7.7	...	7.1	8.4	...	22.0	9.0	...	7.0	7.1	6.6	9.1
Isoleucine........	...	...	8.0	6.5	6.2	7.5	6.3	...	6.0	...	...	4.0	5.3	...	3.0	6.0	4.7	4.5
Valine........	...	...	7.3	6.7	6.6	8.8	5.8	...	5.8	6.2	...	5.0	6.3	...	8.0	4.7	4.2	5.0
Glycine........	...	...	2.2	0.6	...	...	5.0	...	...	8.5	7.2	...	10.3	...	5.6	...	17.4	...
Alanine........	...	...	...	2.8	...	...	4.0	...	...	...	...	...	...	...	...	...	8.8	...
Serine........	...	...	...	7.5	...	...	5.4	4.7	4.9	7.3	...	...	...	...	...	...	...	...
Glutamic acid......	...	...	...	24.2	...	...	15.4	16.5	...	12.2	...	...	24.1	13.1	...	...	21.0	...
Aspartic acid......	...	...	...	6.3	...	...	6.0	...	...	6.9	...	...	...	5.3	...	...	...	...
Hydroxyproline....	...	...	...	0.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Proline........	...	...	...	8.0	...	...	6.0	...	...	...	...	...	...	2.5	...	...	...	...

* Figures taken from Block, R. J.: The Amino Acid Composition of Food Proteins, in Anson, M. L., and Edsall, J. T.: *Advances in Protein Chemistry* (New York: Academic Press, Inc., 1944), Vol. II.

All values are expressed in grams of amino-acids per 16 Gm. of nitrogen, or approximately 100 Gm. of protein.

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Pregnancy.—The increased need for protein in pregnancy is self-evident. Not only must the mother consume protein to provide for growth of fetal tissues but she must store reserve protein for lactation post partum. The need is both quantitative and qualitative since the building of new tissue requires all essential amino-acids in large amounts. The studies of Burke, Harding and Stuart[6] have shown a striking correlation between the protein adequacy of the diet during pregnancy and the infant's condition at birth. According to them, from 10 to 20 Gm. of protein in excess of the normal requirements of the mother should be consumed daily, and on this basis the National Research Council has recommended a daily intake of 85 Gm. of protein. Statistical examination of diets during pregnancy has shown that only 10 per cent of women meet this requirement. It may safely be concluded that wider attention to this matter would pay large dividends by reducing infant mortality and morbidity, for the start in life that a mother can give her child is clearly conditioned by her diet before delivery.

During lactation the drain on maternal protein reserves is no less acute. During the height of lactation a woman may produce 700-800 cc. of milk daily, which corresponds to 10.5-12 Gm. of protein. The protein content of human milk is known to be approximately half that of cow's milk, and the amino-acid content of this protein is well known. Despite this, we have no information regarding the specific amino-acid require-

[6] Burke, B. S.; Harding, V. V., and Stuart, H. C.: J. Pediat., 23:506, 1943.

ments for lactation, except that complete protein is needed. Although the capacity of vegetable sources to supply this need is not known, adequate provision from vegetable sources would probably be difficult or impossible because of the relatively low content of most vegetable foods in essential amino-acids. From this belief rises the familiar recommendation that one half or more of the protein intake during pregnancy and lactation should be from animal sources—meat, milk and eggs.

Trauma.—The problem of nitrogen metabolism in shock is a vast subject inseparably bound to the complex pathologic physiology of burns, hemorrhage and injury which precede the development of the shock syndrome. Despite excellent progress in our understanding of these conditions as a result of intensive investigations stimulated by the war, much remains unknown.

Heavy nitrogen losses resulting from hemorrhage and burns are partially explained by the actual loss from the body of large amounts of protein. In injuries of all types, mechanical as well as bacterial, the excessive catabolism of protein is almost completely unexplained. If adequate protein is given either orally or intravenously to compensate for a theoretical loss from fever and mechanical tissue destruction, the nitrogen balance may nevertheless remain negative for prolonged periods and appears to be unaffected by any therapeutic measures thus far devised.[7]

[7] Committee Report, National Research Council: War Med., 6:1, 1944.

In burns of second and third degree involving up to 50 per cent of the body surface, Co Tui and his associates[8] have shown that there may be a total nitrogen loss of nearly 20 Gm. in 24 hours. This would correspond to 20 L. of plasma or 600 Gm. of meat. In fractures, a total loss of 220 Gm. of nitrogen in 35 days, equal to 1,400 Gm. of protein or 15 lb. of muscle protoplasm, was reported.[9] In meningitis, daily negative balance of 180 Gm. of protein has been demonstrated.[10] In typhus fever, Yeomans and his associates[11] showed a rise in blood nonprotein nitrogen which they believed was closely associated with a destruction of body protein. Madden *et al.*[12] studied nitrogen balance in experimentally produced sterile abscesses in dogs and showed that a strong positive nitrogen balance maintained by the abundant administration of protein assured a high nitrogen excretion as a result of the inflammatory injury. Poor protein nutrition, on the other hand, greatly reduced the urinary nitrogen output associated with the injury, although it did not result in a negative nitrogen balance. These observations led to the assumption that breakdown of protein following injury may serve a useful purpose by providing specific protein fractions used in combating the injury. The depleted individual

[8] Co Tui; Wright, A. M.; Mulholland, J. H.; Barcham, I., and Breed, E. S.: Ann. Surg., 119:815, 1944.

[9] Cuthbertson, D. P.: *Fifth Conference on Metabolic Aspects of Convalescence* (New York: Josiah Macy, Jr., Foundation, 1943); Howard, J. E.; Parson, W.; Stein, K. E.; Eisenberg, H., and Reidt, V.: Bull. Johns Hopkins Hosp., 75:156, 1944.

[10] Grossman, C. M.; Sappington, T. S.; Burrows, B. A.; Lavietes, P. H., and Peters, J. P.: J. Clin. Investigation, 24:523, 1945.

[11] Yeomans, A.; Snyder, J. C.; Murray, E. S.; Zarafonetis, J. D., and Ecke, R. S.: Ann. Int. Med., 23:711, 1945.

[12] Madden, S. C., *et al.*: J. Exper. Med., 82:65, 1945.

would then presumably be at a disadvantage since he is incapable of such a response. Werner[13] proposed that both anabolism and catabolism are increased after injury. It is probable that this phenomenon is under endocrine control in which the adrenal cortex plays an important part.

Surgery.—The trauma incident to anesthesia and surgery of all kinds is regularly attended by protein loss, manifested by a negative nitrogen balance. This has been shown to occur even in such relatively uncomplicated conditions as appendectomy and herniorrhaphy, and the phenomenon is quantitatively more significant with more formidable procedures such as those in chest and gastro-intestinal surgery. In addition to such losses, those involved in blood loss during surgery, loss of secretions through diarrhea and negative pressure drainage of the upper intestinal tract and the losses in serous and purulent exudates must be considered. When the composite effect is superimposed on the poor preoperative nutritional condition likely to be present, especially in patients with chronic diseases, it is not surprising that the duration of convalescence, rate of wound healing and even the final outcome are seriously affected. A greatly improved outlook for the surgical patient may be anticipated with a wider appreciation of these complex factors and increasing availability of the necessary therapeutic materials.

Ulcerations of the Skin.—Both varicose and decubitus ulcers have been shown to be associated with protein

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13 Werner, S. C.: Proc. Am. Soc. Clin. Investigation, p. 36, 1946.

depletion, evidenced by hypoproteinemia. Correction of the deficiency often results in rapid and striking healing, indicating that the nutritional factor may be of fundamental importance in the pathogenesis of these lesions.

Peptic Ulcer.—The use of orally administered protein hydrolysates in peptic ulcer by Co Tui[14] and others has prompted a re-evaluation of present methods of treatment. The Sippy régime provides only 30-40 Gm. of protein daily to patients who frequently already have hypoproteinemia and protein depletion. By increasing the intake to 150 Gm. or more daily striking remissions have been obtained. The nutritional aspect may be the chief therapeutic advantage of the bland meat diet of Holmgren and Meulengracht for bleeding peptic ulcer, in which protein depletion is more severe than in uncomplicated cases. The special advantage of protein hydrolysates in bleeding ulcer has been stressed also by Levy.[15]

Liver Disease.—It is well established that in all diseases involving liver damage and attendant impairment of liver function a derangement of protein metabolism is invariable. This is equally true in cirrhosis, infectious hepatitis and liver damage resulting from exposure to toxic chemical agents. Not only does a high protein intake provide the highest possible liver-regenerating potential in treatment of these diseases, but a deficiency of dietary protein is an important factor in their pathogenesis. The shift in emphasis from carbo-

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14 Co Tui, *et al.*: Gastroenterology, 5:5, 1945.
15 Levy, J. S.: Gastroenterology, 4:375, 1945.

hydrate to protein represents a new point of view based on sound experimental work substantiated by a growing mass of clinical evidence.

The development of Laënnec's type of cirrhosis is a slow, gradual process taking many years, characterized by repeated or continuous episodes of damage to liver cells and regularly associated with poor nutrition. In the typical alcoholic case, the substitution of alcohol for nutritious and protective foods, especially protein, leaves the liver vulnerable to all types of toxic agents. Since 1 qt. of whiskey contains about 2,800 calories, daily intake of this amount so completely satisfies the caloric needs that little or no food of high nutritional value can be tolerated.

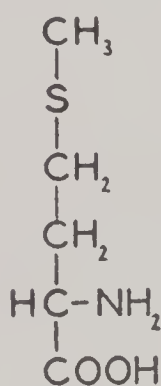Special types of low protein diets have been shown to produce liver cirrhosis in experimental animals, so it is probable that the dietary factor is the principal one in the development of human cirrhosis and it seems justifiable to consider this disease a true deficiency state. In treatment, numerous clinical studies have demonstrated the superior effect of a daily protein intake of 150 Gm. or more.[16] The amino-acid methionine (Fig. 47) is one of the most important protective protein constituents. There is some suggestive evidence that tyrosine serves in the same way. There may also be other, undiscovered, factors in protein food that account for its therapeutic value.

$$CH_3$$
$$|$$
$$S$$
$$|$$
$$CH_2$$
$$|$$
$$CH_2$$
$$|$$
$$HC-NH_2$$
$$|$$
$$COOH$$

Fig. 47.— Methionine.

16 Patek, A. J., and Post, J.: J. Clin. Investigation, 20:481, 1941; Beams, A. J.: J. A. M. A., 130:190, 1946.

In infectious hepatitis there is also strong suggestive evidence that a poor diet predisposes to infection with the virus that causes the disease. This observation was well substantiated during the war, when the epidemiology became of the greatest concern to the Army Medical Corps. Indeed, the dietary factor may account, in part at least, for the epidemic nature of infectious hepatitis during wartime. In therapy, also, the value of a high animal protein intake seems unchallenged, although the effect of methionine alone has been rather disappointing in the few instances in which it could be adequately tried.

Present evidence, both experimental and clinical, indicates the vital importance of protein food, and methionine in particular, in both prevention and treatment of toxic liver damage from such chemicals as chloroform, phosphorus and carbon tetrachloride. In rapidly fulminating cases resulting in acute yellow atrophy, no therapy has been devised that gives dependable results. High quality protein food seems to offer the greatest hope.

Treatment of any of the aforementioned liver diseases therefore should consist in the supplying of 125-150 Gm. of high quality protein daily; this may be provided wholly or partially by the parenteral route, if necessary, as plasma, whole blood or protein hydrolysates. Supplements of methionine in 3-4 Gm. doses daily are also advisable. Completion of caloric requirements should be accomplished chiefly with carbohydrate, so that the fat content does not exceed 60-68 Gm. daily. The low fat intake is advantageous chiefly be-

cause of the greater palatability of the food for patients characteristically troubled with anorexia. In the presence of high protein and adequate carbohydrate, there is no evidence of any special deleterious effect of fat.

Thyrotoxicosis and Diabetes Mellitus.—These two conditions are discussed together because of certain common metabolic aspects. In both there is an abnormal rate of catabolism of body protein to supply energy requirements. In thyrotoxicosis, of whatever specific pathologic type, the elevated metabolic rate places such a demand on fuel foods that, despite greatly increased appetite, the demands for energy balance cannot be met without encroaching on body tissues which, under normal conditions, are protected against destruction by adequate supplies of carbohydrate and fat. In these circumstances the rate of glyconeogenesis, or carbohydrate formation from protein, is increased. The resulting sugar is oxidized for the production of energy and the nitrogen portion of the amino-acids is excreted in the urine as urea to form a negative nitrogen balance. The sources of this catabolized protein are chiefly liver and muscle, the storage or reserve supply always being utilized first. The muscular weakness common in this disease is but one sign of the metabolic drain. Correction obviously depends on a restoration of balance between energy demands, as reflected by the metabolic rate, and energy supply in the form of food. The ideal diet in preparation for definitive treatment must therefore have high caloric value and an abundance of protein of high quality. This becomes especially important if surgery is contemplated, since a good preoperative

nutritional status contributes immeasurably to smooth convalescence and a satisfactory final result.

In diabetes mellitus destruction of body protein may be increased for another reason. The failure of the entire organism to oxidize carbohydrate in a normal manner leads to accelerated conversion of all available metabolites into glucose in an apparent attempt to correct the metabolic deficit by increasing the carbohydrate supply through all available channels. Here also the negative nitrogen balance, commonly seen, leads to the inevitable wasting of body tissues and protein starvation. Restoration of the capacity to metabolize carbohydrate properly by administration of insulin will correct the error, but there is need for large carbohydrate intake in diabetic diets. During early periods of diabetic control this supply should provide at least 1.5-2 Gm. of complete protein per Kg. of body weight.

Starvation.—The syndrome of famine edema has become increasingly well known during both World Wars in which whole populations were subjected to starvation. Both the quantity and the quality of protein food become so deficient that reserves of all food materials are mobilized and the failure of an exogenous supply to replace normal loss of body protein through wear and tear leads to progressive destruction of functioning tissue. The result is a negative nitrogen balance which can be corrected promptly by inclusion of the necessary foods in the diet. In this sequence of events the peripheral phase of protein deficiency, and the one most easily measured, is a fall in circulating plasma protein. Inasmuch as the proteins, especially albumin,

provide the osmotic pressure that balances the hydrostatic pressure of the circulating blood and thereby helps to regulate the exchange of fluid between blood and tissues, any fall in circulating plasma content will disturb the balance and, when carried to extremes, will result in edema. A total plasma protein content of 5 Gm. per cent is sometimes considered a critical level below which edema fluid accumulates, although this is only a relative figure. For a complete understanding of nutritional edema, factors outside the scope of this discussion must be considered to explain the discrepancy often seen between plasma protein levels and the appearance of edema. One of these factors is a change in the capillary wall, probably attributable to malnutrition, so that the osmotic relationships of Starling's law do not apply.[17]

Kidney Disease.—The continuous loss of protein in kidney disease, presumably owing to a faulty glomerular filter, must result in depletion of both reserve and functioning tissue protein unless the dietary intake can be maintained at a high enough level to compensate for the loss. This is usually possible unless the proteinuria is considerable, as, for example, in the nephrotic type of renal disease. In this condition 20-40 Gm. per day or even more of protein may be lost, and massive edema with anasarca is common. In such circumstances it is virtually impossible for the manufacture of body protein to keep pace with the loss, regardless of abundant supply from outside sources. In this disease it has

17 Keys, A.; Taylor, H. L.; Mickelson, O., and Henschel, A.: Science, 103 :669, 1946.

often been suspected that there is a defect for protein synthesis which complicates the simple factor of renal loss. Clinical studies with relatively pure human serum albumin have clearly demonstrated its diuretic effect in a nephrotic child by means of intravenous administration at a speed that greatly exceeds the urinary loss. Such an effect unfortunately is of brief duration, as might be anticipated, since the procedure does not involve any repair of the fundamental renal lesion. Incidentally, the cost and technical difficulties of such a therapeutic program are prohibitive.

There remains among lay people as well as among some physicians an unjustified impression that kidney disease is an indication for a low protein intake. This probably arises from a fear of the accumulation of nonprotein nitrogenous compounds in the blood and the threat of uremia. Since protein will be continuously degraded anyway, regardless of its source, this reasoning is fallacious. Restriction of protein intake for nephritic patients will, therefore, not only fail to delay the appearance of azotemia but will superimpose a deficiency state on an already serious clinical condition. It is much sounder to insure a good protein intake without actually recommending excesses, supplemented by an adequate supply of calories so that the protein-sparing action of carbohydrate especially may allow use of the dietary protein to replenish depleted reserves.

Miscellaneous Conditions.—It is a platitude that a good diet is a prerequisite to treatment of every disease. Nevertheless in certain conditions not primarily deficiency states, special care should be exercised to maintain

satisfactory nutrition because a poor intake of food, either quantitative or qualitative, or both, is especially likely to occur.

In most chronic gastro-intestinal diseases such as peptic ulcer, cancer, chronic ulcerative colitis, amebiasis and intestinal parasitism, the combination of anorexia and dietary restrictions, either self-imposed or recommended by the physician, may lead to superimposed nutritional deficiency. The significance of adequate protein in the diet in each of the conditions is self-evident.

In anemia of all types one must always remember that protein is one of the important constituents from which hemoglobin is made. Although lack of iron is one of the commonest causes of anemia, in some types due to general malnutrition lack of protein may also be a factor. The exact rôle of protein in the genesis of macrocytic anemias is not clearly understood, but poor appetite or poor absorption from the intestine is often present.

In allergies of all types, progressive restriction of the diet is often encountered and frequently results in the omission of important protein foods. This may create difficult dietary problems which tax one's ingenuity, since both quality and quantity of protein intake must be maintained at any cost.

In many psychiatric conditions such as the psychoses and anorexia nervosa, serious self-imposed starvation may occur. The nutritional aspects of such cases are obvious and need no elaboration.

Hyperemesis gravidarum may create an especially difficult problem because of the vital rôle of nutrition

in pregnancy and the neonatal condition of the infant. Indeed, this entire condition is largely one of nutritional management.

In long-continued febrile diseases such as tuberculosis, brucellosis and subacute bacterial endocarditis, an increased catabolism of protein which accompanies the fever combined with a poor appetite tends to create a state of malnutrition which, from its protein aspects, may seriously impair the patient's immunologic potential and lead to unfortunate or even serious consequences.

Administration

It is often possible, especially when the appetite is good, to correct a subnormal intake of protein by changing the diet. In many clinical conditions, however, particularly those associated with marked anorexia or an excessive or urgent need for a high protein intake, supplementary administration is desirable or necessary. This may take the form of plasma, whole blood or amino-acid preparations.

For oral administration it is usually sufficient to insure a quantitative intake calculated from the requirements of the individual patient, based on size and the metabolic demands of the clinical condition. The dietary sources of the protein should be varied, with at least 50 per cent derived from animal foods; it is seldom necessary to be concerned with the specific constitution of these foods. Table 13, showing amino-acid composition of common protein sources, has therefore more interest than practical value, but it does illustrate the

inadequacy of some commonly available food sources.

Special proteins are helpful in some circumstances. Milk, for example, contains two particularly valuable proteins, casein and lactalbumin, which are especially adapted for nutrition of the infant. The complete assortment of amino-acids in milk, with the possible exception of tryptophan, its instability in the chemical sense and consequent ready digestibility and its precipitation by acids and rennin give it remarkable value as a protein source in a variety of conditions. Its excellent content of the sulfur-containing amino-acids cystine and methionine make it an important food in all types of liver disease. Numerous modifications of milk, its proteins and especially casein are found in a variety of cheeses and prepared, preserved or modified infant foods. The one outstanding deficiency of milk in nutrition which must be kept in mind is its low iron content, but supplements of simple inorganic iron compounds will make good this lack.

For regeneration of blood proteins, liver, milk and beef muscle protein have unusual value. The occurrence in liver of iron, specific antianemic factors, all of the known vitamins and labile proteins is important in this connection, but the high biologic value of the proteins is equally significant.

Massive intravenous use of human blood proteins was explored thoroughly during World War II, and its value is unquestioned both in shock and shocklike states, for the physicochemical restoration of normal physiologic conditions, and in protein malnutrition with poor appetite, vomiting, diarrhea and other complica-

tions which preclude an adequate oral supply. Many liters of human plasma have often been given during each 24 hour period, and there is no doubt that this measure was life-saving in many instances. Each liter of pooled human plasma is calculated to provide about 70 Gm. of high quality protein, or the estimated daily requirement for a man of average size. If the supply of plasma can be guaranteed, there is every reason to believe that human beings can be maintained in positive nitrogen balance for indefinite periods by this means, accepting, of course, the technical burden of intravenous administration.

Protein digests containing all of the essential amino-acids may be given by mouth. The one possible advantage of this procedure is the avoidance of the necessity for digestion in the intestine. Absorption can proceed immediately. Unfortunately these preparations usually have an objectionable taste that cannot easily be disguised with fruit juices or other flavoring materials. Nevertheless they have been used successfully in a variety of clinical circumstances. By administration of 15 or 20 Gm. of the mixture dissolved in water at intervals throughout the day it is possible to achieve an intake of 150-200 Gm. of protein in 24 hours. Occasionally tube feeding of similar amounts is helpful and eliminates the unpleasant taste.

Intravenous administration of amino-acids has received increasing attention in the past five years; the subject was completely summarized by Elman[18] in 1944. Human subjects can be maintained for long periods in

18 Elman, R.: Physiol. Rev., 24:372, 1944.

good nitrogen balance with amino-acids administered intravenously as the sole source of protein. The preparations for the most part have been produced by the acid or enzyme hydrolysis of milk or pancreas protein. Several such digests are available commercially. Administration of amino-acid preparations by mouth results in greater utilization than does intravenous injection because of the anatomy of the portal circulation which leads the products of intestinal absorption directly to the liver before they are released into the systemic circulation. Intravenous use permits a larger excretion of unchanged amino-acids in the urine, although Emerson and Binkley[1] found it not to exceed 10-30 per cent of the administered dose when only the 10 essential amino-acids were used. A considerable portion of the amount wasted may have been the unnatural isomers contained in the mixture which are slowly or incompletely utilized. Other estimates of this wastage are considerably higher, but the measurable retention of nitrogen and the rise in blood proteins following this method of administration indicate that there is good utilization.

Two amino-acid preparations are available for general use, Amigen (Mead Johnson) and Parenamine (Stearns). The latter is supplemented by tryptophan to compensate for the low content of natural casein digests. For intravenous use these preparations are usually diluted with 5-10 per cent glucose in normal saline so that the final concentration of amino-acids does not exceed 5 per cent. This technic provides carbohydrate for its protein-sparing action and also reduces

the nausea and vomiting that may occur when higher concentrations are used. For the same reason, adminis-ration must be slow; two hours should be allowed for the giving of 1 L. of solution. Despite these precautions chills and fever may accompany the injection and long-continued use may result in thrombosis of peripheral veins. These difficulties may be avoided in the future when mixtures of pure amino-acids become available. During parenteral administration of protein hydro-lysates special care must be taken to guard against bac-terial contamination; the solutions are excellent culture mediums and failure to observe this precaution prob-ably accounts for many of the pyrogenic reactions that have been encountered.

Protein hydrolysates may also be given by subcuta-neous injection, although their absorption and utiliza-tion are obviously much slower. Solutions should be made isotonic with blood and must be neutral in reac-tion. To do this, Elman recommends dilution of a so-lution containing 5 per cent amino-acid and 5 per cent glucose with an equal volume of distilled water. Other-wise their action is similar to that of glucose given by the same route.

It may become necessary, at times, to choose among plasma, whole blood and protein digests for intravenous therapy. More often they may be considered supple-mentary. Both plasma and whole blood immediately provide pre-formed whole blood protein for use in acute emergencies in which restoration of circulating blood volume may be life-saving. If such an emergency is due to hemorrhage, the replacing of red cells may be as

important as the supplying of protein, in which case whole blood transfusions are certainly indicated. In certain other circumstances involving both an acute immediate need and protein starvation, both plasma and amino-acids may be given the same patient. Thus each case must be considered a special problem and therapy planned accordingly. There is every reason to hope that the quality of protein digests will be steadily improved to the point where their administration by injection will offer no greater therapeutic obstacle than the similar use of glucose. It may even be hoped that fat emulsions can eventually be added to the therapeutic armamentarium and thus make possible the maintenance of the entire nutritional needs of chronically ill patients by parenteral injection.

FUEL FOODS

As suggested in the last section of the preceding chapter, the animal body never stops producing heat while life continues. No chemical process is more fundamental or vitally important. The preferred source of this heat is the oxidation of fat and carbohydrate. If adequate amounts of these two fuels are furnished, the body will oxidize protein only when it is eaten in excess of the needs for building tissues, etc. The degradation products from protein substances which have been destroyed in metabolic processes are also burned. The amounts of fat and carbohydrate oxidized depend to a small extent on the available supplies of these compounds, save that in addition, each has a slight specific dynamic action, far less, however, than in the case of protein. The determining factors of the total heat production are basal metabolism (thyroid control and other forces), performance of external work, stimulation by hormones such as the posterior pituitary, anterior pituitary or adrenal medullary secretions, and alterations in body temperature. The summation of these demands sets the level of total oxidative processes for which fuel is secured from circulating glucose and fats or from the stores in fat deposits, glycogen reserves or proteins.

The total heat production of children or adults varies from about 1,000 to well over 5,000 calories per 24 hours. However, it is unusual to find a situation in which an adult requires more than 4,000 calories to maintain normal weight while engaged in vigorous work. The known capacity of the human body to use carbohydrate and fat can provide for the production of about 1,300 calories per day by an individual weighing 75 Kg., at rest. During muscular work this total would be greater. The margin of reserve capacity is evident. In health the ability to oxidize carbohydrate as the sole source of this energy is adequate for all ordinary needs. The degree to which the body may depend on fat oxidation as the only source of heat is limited. The oxidative metabolism of the brain requires largely, if not entirely, glucose as fuel. Other organs, such as heart and liver, use glucose continuously if not exclusively. The mechanism of fat oxidation involves another limiting factor, spoken of as ketosis.

During the oxidation of fatty acids, derived from fats by enzymatic hydrolysis, the large molecule of very stable and water-insoluble acid is broken into a number of smaller, water-soluble fragments which can be more easily oxidized. One of the most important molecules is acetoacetic acid, a very labile compound. Successful combustion of acetoacetic acid seems to depend on processes in the peripheral tissues. The amount which can be disposed of per day by a resting body is said by Stadie to be about that which comes from 3 Gm. fat per Kg. body weight. This

would correspond to about 27 calories per Kg. per day. If the use of fat exceeds this rate, acetoacetic acid will be incompletely used and be found to accumulate until easily detectable amounts are found in the blood and urine. Under such circumstances, acetoacetic acid is converted in part to beta hydroxybutyric acid, less reactive and toxic, and in part to acetone, still less reactive and toxic. Acetone is the best known and most easily recognized of these three compounds, which have come to be known as ketone bodies. Ketosis is the accumulation of these substances until clinical tests detect their presence in urine or, in the case of acetone, in expired air. The acid nature of acetoacetic and beta hydroxybutyric acids leads to the neutralization of part of the bicarbonate in the circulating blood and in tissue fluids, as a consequence of which ketosis produces acidosis. It is because of these circumstances that the occurrence of ketosis marks the upper limit to the use of fat as a fuel. The extent to which the capacity to use fat is increased during exercise is still unknown. It is certain that fat can be used without ketosis to furnish at least two-thirds of the energy requirements. From these considerations it can be understood that ketosis can be prevented by making available sufficient carbohydrate or protein so that the total demand for fat oxidation does not exceed 3 Gm. or 27 calories per Kg. per day.

One of the amazingly accurate adaptations of energy economy in the animal body is the balance which is maintained between the intake of fuel food

and the expenditure of energy in most individuals. It would be difficult to calculate and predict the amount of food needed for the type of activity characteristic of most persons. It might therefore be anticipated that disproportions between calorie intake and expenditure would be frequent, resulting in fluctuations of body weight. Common experience is that most individuals have only slight fluctuations of weight. This suggests that the appetite and urge to activity must be nicely adjusted. The mechanism of this adjustment is not entirely understood. Hunger does increase following exercise or reduced food intake. But when no restriction is set on the intake of food many persons eat far more in terms of calories than is necessary to maintain their weight equilibrium. This has been proved by deliberate restriction of intake without loss of weight, while the activity is continued. There exists some regulatory mechanism by which the unnecessary excess of food is disposed of through increased oxidation and dissipation of the energy as heat or work. This provision for use of extra food without gain of weight has been termed *Luxus Konsumption* by German students of nutrition. It is believed that imperfections in the process are a cause of obesity, but the anatomic location of the controlling mechanism is still undecided. It seems equally possible that overactivity of this same process may account for the difficulty experienced by others who remain exceedingly slender despite persistent attempts to gain weight by eating much and doing little voluntary work. The significance of the hypothalamus in

weight regulation is the subject of considerable current study in the hope of developing better understanding of these problems.

The body is capable of deriving its energy from an extremely varied mixture of fuels. For several hours, or even a few days, carbohydrate may be almost the entire source of heat. Theoretically, protein might be used as a sole fuel, but this would be so expensive, would involve the excretion of so much nitrogen and would be so difficult to arrange (to avoid fats which occur in all natural high protein foods) that all-protein diets are never used. Attempts to use nothing but fat as fuel will induce ketosis and will lead to increasing mobilization of body proteins. The practical diets of the population at large or of patients under medical control are made up of mixtures of protein, carbohydrate and fat. The proportions of these three components may vary widely without significant disturbances in nutrition. The details of carbohydrate and fat need and supply may best be discussed separately.

Alcohol as a Fuel

Since it is known that about 90 per cent of the alcohol ingested is oxidized, and since the heat-equivalent of alcohol is 7 calories for each gram, it is often said that the total energy intake of anyone may be calculated by adding to the totals for protein, carbohydrate and fat the product of the amount of alcohol times seven. For purposes of nutrition this is done with the assumption that the oxidation of

alcohol in the body serves to replace the oxidation of one or more of the three other fuels. There is, consequently, mention of the fat-sparing or carbohydrate-sparing action of alcohol. This replacement of fuel foods leads to one of two results: obesity, if the usual foods are taken in addition to the alcohol, or risk of undernutrition with respect to protein, minerals and vitamins if the usual foods are not taken. The oxidation of alcohol depends on the size of the body, and most especially on the size of the liver, where oxidation of alcohol is initiated. Increase in exercise does not increase the rate of this oxidation. Use of thyroid hormone or of oxygen inhalation does not augment the production of calories from alcohol. It therefore seems probable that alcohol does not serve as a fuel for muscular activity, but that the heat produced from its oxidation is a substitute for combustion of carbohydrate and fat by the liver and other nonmuscular organs. The use of large amounts of any alcoholic beverage by a sedentary worker is accompanied by more risk of nutritional disturbance than is the case in one who is performing vigorous physical labor. This is not because of the use of alcohol as fuel for work or faster elimination of the substance, but because the active individual must have more total fuel and hence eats a larger amount of usual foods, with their accompanying minerals and vitamins. One of the great risks of chronic alcoholism is the reduction in intake of the food factors which are not provided by distilled spirits.

Alcohol exerts a depressing effect on the central

nervous system and on many other tissues. In any calculation of energy balances this depression introduces a factor which cannot easily be discounted. With these uncertainties we can only conclude that it is not justifiable to calculate calorie production for alcohol just as for the other fuels discussed. In clinical considerations of nutrition, the rôle of alcohol as a source of bodily energy is open to question. The effects of alcohol on appetite and vitamin intake and its etiologic responsibility in certain clinical disorders are discussed in the chapters dealing with the vitamin B group.

Another side of the nutritional aspect of alcoholic beverages is presented by the carbohydrates in malt liquors and wines. These carbohydrates are the unfermented material from the grain and fruit and are available as food. The carbohydrate content of malt liquors is 3-6 per cent as compared with an alcohol content in the same range. Of the wines, the dry types contain 1-4 per cent, the sweet ones 8-20 per cent of sugar. Brandy, the cordials and liqueurs contain sugar added to concentrations of 30 to 35 per cent. Although the amounts of sugar consumed with small portions of these last beverages may be inconsequential, the sugar content of wines may not be ignored in any careful dietary calculations. The larger amounts of malt liquors frequently used would include enough carbohydrate to constitute a significant part of the day's requirements. In addition, these malt beverages furnish large amounts of some of the factors of the vitamin B group, and by this content plus

their taste serve as stimulants of appetite. It is by these combined effects that malt liquors are so often fattening. The slight sedative effect of the alcohol tends to reduce activity, thereby facilitating a gain of weight. If alcohol can be used as a substitute for other fuels, this further factor would also tend to contribute to the weight increase so commonly seen among those who drink much beer.

CARBOHYDRATE

The Need

1. Why is carbohydrate required? Carbohydrates are needed as the source of glucose, the circulating sugar, which supplies all tissues with a fuel which can be quickly oxidized in the presence of the several enzyme systems described in the chapters on vitamin B fractions. Sugars are also utilized as constituents of such special complex molecules as nucleic acid, mucin and lipoids in nerve tissues. Glucose is converted into the glycogen of liver and muscle and is the precursor for hexose phosphates, materials which are integral parts of the contraction and recovery mechanism of muscle. Lactose is made by the mammary glands from glucose. Among other derivatives of glucose is glycuronic acid, used for conjugation with toxic materials of the phenolic type, in preparation for excretion.

If there is insufficient intake of glucose, protein from food or tissues is converted in part to glucose. Excess dietary protein, not necessary for growth or repair processes, is similarly transformed to sugar. This chemical change is called gluconeogenesis. It is catalyzed by the adrenal cortical hormone. Under certain conditions the glycerol of fats may be converted to glucose. There are thus two sources for

glucose other than preformed carbohydrate. It is only under exceptional dietary restrictions that these sources account for more than a minor fraction of the glucose formed or used in the body.

The animal body has become adapted to an operating blood glucose concentration of 80 to 100 mg. per 100 cc. Decrease below the usual minimum level leads to prompt activation of regulating forces, which tend to restore the circulating sugar from glycogen stores or from protein. Increase above the usual level is followed by increased rates of utilization, storage or, if the increase is above the threshold level, usually around 170-190 mg. per cent, a resort to urinary excretion of glucose. The body is elaborately equipped to maintain at all times the optimum concentration of this indispensable fuel in the blood and intercellular fluids. This regulation is an example of Cannon's homeostasis, the maintenance of a constant environment for the cells.

2. When is carbohydrate required? The amount of glucose in the blood is depleted sufficiently in one hour by supplying tissue oxidation demands so that the homeostatic mechanism is set in action. As long as the glycogen stores are adequate, this renewal of blood sugar will proceed. But the best stocked liver would have lost its glycogen reserves after 24 to 48 hours of replenishing the blood sugar. This is apparent if the problem is expressed in quantitative terms. A 1,500 Gm. liver containing glycogen to the extent of 4 per cent would provide 60 Gm. of glucose, equivalent to 240 calories of energy. It is not difficult to see, there-

fore, how rapidly this reserve supply of fuel would melt away under conditions of even moderate physical activity. For this reason, at least a daily carbohydrate meal is indicated to maintain the liver glycogen. If the hepatic stores are not renewed at short enough intervals, fat and protein will be mobilized, with consequent ketosis and increased protein catabolism. The normal blood sugar level will be maintained for weeks during such an undernutrition period, but at the expense of protein catabolism.

Hunger serves to induce the taking of meals at shorter intervals than once daily, thereby avoiding the risks of allowing serious depletion of glycogen stores. The series of processes which determine the recurrence of hunger are dependent chiefly on sugar metabolism. During the two to four hours following the ingestion of any carbohydrate food there is absorption of glucose from the gut, producing an increased concentration of glucose in portal blood. This affords an augmented supply for the storage of glycogen. Some of this temporary excess of sugar is oxidized at once in all tissues, thereby reducing the amount of fat which was being burned previously. Further amounts of glucose are converted to fat in the depots. Arterial blood glucose concentration is increased because not all the sugar is removed in the first passage through the liver. The increased blood sugar concentration stimulates the pancreas to the secretion of a greater amount of insulin, which catalyzes a more rapid use of glucose from the blood than would otherwise occur. The consequences, as

seen in the blood sugar concentration, are a rising level of sugar for the first half to one hour during absorption, followed by a rapidly falling level during the second hour. Sometimes this fall continues for a longer time. This falling blood sugar level, occurring while absorption is still proceeding, indicates that utilization of glucose from the blood is more rapid than addition of glucose to the blood from the gut. If this reduction in circulating sugar level proceeds to a concentration below the optimal, glycogen will be reconverted into sugar by the liver, to maintain the sugar level in the blood. When this response by the liver is tardy or inadequate, the lower blood sugar concentration stimulates hunger contractions in the gastric muscle and irritates hypothalamic centers in the brain. This latter process leads to impulses which pass down the autonomic nerves, giving rise to increased secretion of epinephrine and to augmented stimulation of hepatic hydrolysis of glycogen to glucose. This nervous reflex response serves as the second line of homeostatic defense against unduly low blood sugar content. The autonomic nervous activity and epinephrine secretion add emotional intensity to the hunger sensations in the stomach and thus increase the desire to secure more food. In this way we tend to become hungry because we have recently eaten. Unwise indulgence in response to such hunger is the basis for some cases of obesity.

Whenever this series of alterations in sugar levels occurs slowly and when small sugar changes serve as adequate stimuli for prompt operation of the

homeostatic mechanisms, symptoms are slight or absent. When the changes in blood sugar content are greater before responses occur, hunger is apt to be felt, and in exaggerated cases, the evidences of increased autonomic activity and epinephrine secretion are recognized, with tachycardia, tremors, sweating and emotional instability. These same phenomena appear after injection of excessive insulin in the therapy of diabetes for similar reasons, i.e., a deficit of circulating glucose.

Such reactions are surprisingly common in normal people—produced by the physiologic mechanism described; but, regardless of their source, they may be accompanied by marked emotional reactions of anger or irritability which can be promptly relieved by eating, especially by eating carbohydrate food. The phenomenon of hunger is very complex, of which the falling blood sugar level is only one component mechanism. However, it should not be inferred that all hunger is brought about in this way. In the adult body well adjusted to modern living habits, hunger does not appear until three or four hours after a meal. In very young children, hunger appears sooner. The conscious hunger reaction is especially characteristic of youth. Sometimes this occurrence of marked hunger associated with hypoglycemia (low blood glucose concentration) persists into adult life and causes enough discomfort to necessitate eating at intervals of two to three hours throughout the day. The demand for sugar supply at such short intervals may be gratified by foods of almost any type. Such convenience will de-

termine the conduct at these times of hunger reaction. Hypoglycemic hunger can be greatly reduced, in many cases entirely avoided, if the meals are planned to contain only 25-40 Gm. carbohydrate and if at the same time they contain sufficient fat to cause a slight delay in digestion and absorption of the food. When diets follow such a plan, the blood sugar level does not rise as high or fall as rapidly during the hours immediately after the meal.

The physician must be alert to provide carbohydrate food in any type of illness or any postsurgical situation in which food intake is interfered with. The most urgent needs of the body for nutriment may be listed in the following order: oxygen, water, glucose, sodium chloride. Under various types of pathologic conditions, it may be necessary to prescribe any one or all of these in definite amounts. Since the demand for water, sugar and salt is continuous and urgent, the patient must not be allowed to go longer than 24 hours without them. The use of dilute glucose solutions, usually 5 per cent hypodermically, rectally or intravenously, makes it possible to furnish any patient with enough sugar to prevent both ketosis and exaggerated nitrogen catabolism. It would be difficult to furnish in this way all the calories needed for weight maintenance, but that is seldom necessary for the brief periods before feeding can be resumed. For several reasons it is wise to divide the daily intake of such parenterally administered sugar into two or more doses. Glucose solutions may be combined with saline or other liquids as desired.

3. What kind of carbohydrate is required? The digestive tract will produce glucose from starch, glycogen, maltose, dextrins and lactose and sucrose. The galactose and fructose remaining from the hydrolysis of the last two sugars are converted into glucose after absorption or are used in part as substitutes for it. The carbohydrates just mentioned are considered the only important food sources of sugar. Other carbohydrates, especially cellulose and hemicellulose, are important constituents of vegetable fibers but are not digested in the human alimentary tract. Save for partial fermentation of some of these substances, as a consequence of which water-soluble organic acids are formed in the gut, these cellulose carbohydrates can be ignored as nutrients. Whether the products of fermentation are of nutritive value in the human is unsettled.

As sources of glucose, it is immaterial for the adult which carbohydrates are eaten. On the quantitative side, however, too large amounts of preformed sugars may make the food too sweet, interfere with appetite, cause excessive fermentation in the bowel or lead to perverted tastes. The taste for sweets is entirely acquired, not a natural appetite. The rate of hydrolysis of starch and of the disaccharides, sucrose, lactose and maltose, is so rapid that any of these carbohydrates will give quickly available sugar for immediate needs. In fact, because the rate of absorption of fructose, one of the component sugars of ordinary cane sugar, is appreciably faster than that of glucose, hypoglycemia is most promptly relieved by

sucrose, even though it must be hydrolyzed first. Choice between various carbohydrates is therefore made on the basis of taste and of dietetic plans. In infant feeding it may be important to specify the type of sugar used because of the effects on intestinal fermentative flora.

For parenteral injection, the only sugar used is glucose. The disaccharides are not hydrolyzed in the blood stream and hence when injected directly are excreted promptly as foreign bodies by the kidneys. Fructose and galactose are more expensive and offer no advantages to recommend their use parenterally.

4. How much carbohydrate is required? The total need for carbohydrate depends on the amount of fat used. These two foods must provide nearly the entire caloric requirement for the day. The ingestion of 750 Gm. carbohydrate would provide, at 4 calories per Gm., a total heat production of 3,000 calories. This requirement could be satisfied by the use of three 1 lb. loaves of bread, not an impossible, but perhaps an uninviting, task. Other foods with lower carbohydrate content would be required in larger amounts. In common practice these carbohydrate foods are eaten in smaller amounts because of the accompanying use of fat foods. Each gram of fat supplies 9 calories and thereby materially reduces the need for carbohydrate.

The minimum carbohydrate need is defined as the least amount which will prevent ketosis. This varies with body size and with activity and other factors which affect total metabolism. Actual requirements vary between 50 and 100 Gm. per day. The smallness

of these amounts is surprising to many clinicians. Successful maintenance of diabetic patients on such carbohydrate intake over long periods has proved that all the needs of the body can be met with such a small quota of sugar if at the same time the fat intake is high enough to provide total calories to balance the energy output. Between the limits of this minimum need and the maximum, as represented by enough carbohydrate to supply the total energy requirement, the diet may include as much or little carbohydrate as is desired. However, there is one further limiting factor which must not be forgotten, namely, the need for unsaturated fatty acids and for fat-soluble vitamins, as discussed in Chapter XVI. With this need and the practical advantages of a mixed diet, no one attempts to use diets made entirely from carbohydrate. The rice-eating Orientals use a high proportion of starch, with moderate protein and low fat intake.

Sources

The common sources of carbohydrate in the diet are cereal grains, potatoes, fruits, vegetables, nuts, milk, refined sucrose, syrups and honey. The cereal products vary from 50 to 90 per cent in starch and sugar content, whereas potatoes contain only about 20 per cent starch. Milk is 5 per cent lactose. The composition of nuts varies widely. Fruits and vegetables vary from less than 3 to 20 per cent of available carbohydrate content. They are grouped for convenience into those which represent 3, 6, 9, 12, 15 and 18 per cent carbohydrate. These figures are ap-

proximations and averages, since all natural foods occur with considerable variation in carbohydrate content. The syrups contain about 70 per cent, honey about 80 per cent sugar.

SPECIAL PURPOSE CARBOHYDRATES

Glucose (officially known in American medicine as dextrose) is the form in which most carbohydrate circulates and is used in physiologic processes. Consequently, all injections given parenterally for the supply of carbohydrate food are prepared from glucose. A solution containing 5 per cent of this sugar is so nearly isotonic with blood that it may be used freely for any type of injection and may be mixed in any proportion with other isotonic fluids prior to administration. Such glucose solutions are conventionally sterilized by heating in an autoclave. If the temperature is too high or the heating too long, the solution will become discolored owing to the formation of caramel. In addition, organic acids are formed. These are known to be responsible for many reactions following intravenous use. When the solution is heated at 5 lb. pressure for not over 20 minutes, this caramelization does not occur to a significant extent. Any solutions which show appreciable color after autoclaving should be rejected to avoid reactions following injection. One further important factor in the preparation of solutions, not only of sugar but of any substance to be injected intravenously, is the use of water which has been distilled in such a way as to eliminate contamination with pyrogenic

materials. These pyrogens (fever-producing sub-stances) are heat-stable bacterial products which per-sist in contaminated water despite boiling. For this purpose the water must be doubly distilled, or better, the distillation carried out in a still so arranged with baffling devices that the mechanical entrainment of spray cannot carry nonvolatile pyrogen over to the distillate. The distilled water must then be kept in sterile containers until used or the solutions prepared and autoclaved within a few hours after the water has been distilled. When such precautions are fol-lowed, the glucose solutions may be used with safety by subcutaneous or intravenous route in any amounts which are needed and which will not embarrass the circulation or unduly distend the areolar tissues under the skin.

The administration of 5 per cent glucose solutions by rectum, as continuous drip or as repeated small retention enemas, is an easy way to provide nutrition for many patients who cannot swallow even liquid foods with comfort or safety. These glucose solu-tions need not be sterilized or even be made from highly purified glucose. The presence of small amounts of dextrin, coloring matter or other impuri-ties found in commercial corn syrups is no obstacle to the use of these inexpensive sources of glucose when granular or crystalline glucose is not readily at hand. Although they contain about 70 per cent carbohydrate, all of which is available when the syrup is taken orally, only about half of this is in the form of glu-cose and therefore assimilable through the mucosa of

the colon. To prepare isotonic solutions of such corn syrup, it is advisable to dilute the commercial syrup with about seven times its volume of warm water. This can be used as a 5 per cent solution of sugar. Cleansing enemas should precede the injection and should be continued until the return is clear. Attention to the comfort of the patient in such matters as the size of the rectal tube, rate of administration, temperature of the solution and changes of position will make it possible to use rectal sugar administration for many hours. The amount of any rectal injection which can be absorbed will vary with the relaxation of the bowel. The rate of administration is frequently over 100 cc. per hour, thereby introducing 5 Gm. per hour, which in 12 to 15 hours will provide the minimum needs for a day. Despite denials of the efficacy of this method, the prevention of starvation ketosis by such therapy proves its dependability.

The use of highly concentrated solutions of glucose, usually 50 per cent, is convenient for the rapid administration of the sugar to relieve hypoglycemia produced by overdoses of insulin or to introduce sugar into the circulation of a patient who should not be burdened with any large increment of fluid because of myocardial inadequacy. Rapid diffusion of the injected glucose into tissues, prompt oxidation of much of it and dilution of the remainder in the total volume of circulating blood serve to reduce the osmotic pressure of such concentrated solutions when they are given in amounts of 25 to 100 cc., and therefore the marked increase in circulating blood volume

which might be anticipated does not occur. If the injected sugar is sucrose, it remains in the circulation without oxidation and tends to draw water from the tissues, thereby increasing blood volume, but it is ultimately excreted unchanged in the urine. This use of intravenous sucrose to reduce edema should not be repeated, especially in patients with renal damage, for it irritates renal epithelium.

Lactose is of special importance in feeding carbohydrate because it has a low sweetening value and because its presence in the intestine supports a flora which produces a mildly acid reaction and stimulates intestinal motility. The low sweetening power is sometimes of value in adding more calories to drinks which are not palatable if they are too highly sweetened with glucose or sucrose. The alteration of intestinal flora by substitution of lactose for some other carbohydrate has been the basis of several types of dietotherapy for constipation, intestinal putrefaction and various ailments attributed to these disturbances.

Limitations of Carbohydrate Intake

There are three principal conditions in which it becomes important to limit the amount of carbohydrate food. These are diabetes mellitus, recurrent hypoglycemia and obesity. In diabetes the essential physiologic difficulty is a reduced ability to use glucose. The most obvious way to treat the condition is by limiting the intake to the amount which can be used without abnormally high blood sugar concentration, substituting fat for the balance of the calories

needed. In more than half the diabetics who have been treated in this way, such a plan has sufficed for the maintenance of normal weight while the individual continues with his usual employment. When the restriction of carbohydrate cannot be pressed to the point of normal blood sugar level without the appearance of ketosis, it becomes necessary to inject insulin, thereby increasing the rate at which the body can use glucose.

Following the widespread use of insulin, it became apparent that one might use large amounts of carbohydrate in the diet of even the diabetic with a severe form of the disease, if the amount of insulin injected was increased to prevent hyperglycemia and glycosuria. A number of clinicians have explored the possibilities of feeding all diabetics under their care these so-called higher carbohydrate diets for years. The total daily carbohydrate intake varies from 150 to 400 Gm. in different clinics where this is done. Among the advantages claimed are an increased feeling of fitness and physical vigor, satisfaction in being able to choose one's foods more like the ordinary individual does and relative freedom from the sense of restriction of being on an obvious diet. These are all subjective and therefore difficult to debate. On the contrary, many patients who have used the high fat, low carbohydrate diets report the same subjective satisfactions except for the obvious limitation to a prescribed menu. The physiologic advantages claimed for the higher carbohydrate ratio include protection of the heart, arteries, liver and nervous system

from the risks of deficient carbohydrate metabolism. Evaluation of these criteria is also difficult. There is certainly no published evidence to show that the prolonged use of a high fat diet, without ketosis or persistent glycosuria, is a factor in the cause of arteriosclerosis, myocardial failure, hepatic disease or degenerative disease of the nervous system. The level of blood cholesterol is known to be elevated in diabetes which is not adequately controlled, but when blood sugar content is brought down to proper levels and weight maintenance of the diabetic established, the cholesterol content of blood returns to normal levels. The occurrence of cholesterol in many fats has led to a fear that high fat diets contributed to this difficulty, and therefore high fat diets have been shunned. This argument has been strengthened by the knowledge that arteriosclerotic lesions contain much cholesterol. The situation may be clarified by pointing out that blood cholesterol content is not kept high on a high fat diet or even a high cholesterol intake and that the body can make cholesterol in large amounts even when there is no cholesterol eaten.

Another approach to this debate is through the changes in the tolerance for sugar which can be demonstrated after individuals are maintained on diets high in carbohydrate, fat or protein, respectively. The tolerance curves are shifted to indicate a reduced ability to use sugar promptly when the diet has been high in fat. Therefore the high fat diet is held to be a disadvantage to the diabetic, whose sugar tolerance is already subnormal. Attempts were made

to use a high carbohydrate diet to improve the tolerance of the diabetic, i.e., to increase the amount of sugar he can use per day unaided or to reduce the amount of insulin needed per day. These have been reported as successful in some cases, failing in some and equivocal in still others. It is well recognized that the normal physiologic stimulus to the pancreas for insulin production is carbohydrate food, and there is reason to believe that this rule applies also to some types of diabetes. It is obvious that any plan of diabetic management which includes the maintenance of normal body weight, with freedom from hyperglycemia, frequent glycosuria and ketosis, is certain to be marked with a number of cases demonstrating recovery of sugar tolerance to various extents. It is extremely difficult to draw from such evidence any conclusions which will apply to all diabetics. Attention should be called to the fact that some dietary régimes which have produced a striking reduction in sugar tolerance have been so high in fat and low in carbohydrate that they have induced ketosis; it is unjustifiable to attribute the change to the fat-carbohydrate ratio alone. All proposed diet schemes for diabetics demand freedom from ketosis.

The proper ratio of fat to carbohydrate in these diets is therefore still under debate, as it has been for decades. In a general survey of theories of diabetic management it is possible to divide the dietary schemes into three main categories. One extreme is the high fat diet, generally referred to as the Woodyatt diet, since it was first proposed by Dr. Woodyatt of Chicago. Under this plan, the dietary carbohydrate is reduced to

a minimum consistent with the avoidance of ketosis, and the main caloric supply is derived from fat. It is based primarily on the premise that since diabetics are unable to utilize carbohydrate, they should be given the smallest possible amounts consistent with health. A typical Woodyatt diet would be: protein 60 Gm., fat 190 Gm., carbohydrate 80 Gm.

At the other extreme is the high carbohydrate diet, as advocated by Rabinowitch of Montreal. This is based on the belief that the constant stimulation of the insulin-producing capacity of the pancreas through an abundant supply of sugar will result in a maximum restoration of the metabolic defect toward normal. Diets in this category typically contain protein 70 Gm., fat 45 Gm., carbohydrate 350 Gm.

The diabetic management advocated by Joslin of Boston consists of diets intermediate between these extremes and combining many of the advantages of the other two. Diets of this type contain protein 70 Gm., fat 100 Gm., carbohydrate 200 Gm.

Each of these plans of management has its advocates, its advantages and its disadvantages. Of the three, the intermediate type of Joslin has unquestionably been most widely accepted and is in greatest use by physicians everywhere. A detailed critique of diabetic management is outside the scope of this volume, but it may be stated in support of the Joslin diets that they have the great advantage of being most nearly like the diets of normal, healthy people and for this reason contribute greatly to the comfort and ease of management of the patient. The practice of preparing

"tailor-made" mixtures of protamine and standard insulin and the availability of some commercial mixtures of this type have significantly reduced the hazard of sharply fluctuating blood sugar levels which may be encountered with any type of diabetic diet, so that good control may now be attained in most patients by using a moderate carbohydrate intake and one injection daily of insulin.

It is not yet possible, despite the decades of experience and investigation on which to base an opinion, to settle this difficult problem of diabetic management. Indeed, new information derived from experimental diabetes in animals has revealed that the entire problem of carbohydrate metabolism, pancreatic islet function and biologic oxidation is much more complex than was originally believed when insulin first became available for clinical use more than two decades ago. We now know for the first time, from the work of Cori and his co-workers,[1] of at least one biochemical function of insulin, in terms of the enzymatic degradation of glucose. We may hope that this represents the first step in the actual solution of the mystery of the abnormal metabolism in diabetes mellitus. Until such a solution is found, however, dietary measures will continue to be of the utmost importance in the practical management of that disease.

Hypoglycemia, resulting usually from an excessively rapid removal of glucose from the blood, may demand additional supplies of sugar for the immediate

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[1] Price, W. H.; Cori, C. F., and Colowick, S. P.: J. Biol. Chem., 160: 633, 1945.

relief of acute symptoms. Hypoglycemia occurring erratically or for prolonged periods is probably related to tumors in the pancreas. In such cases the frequent administration of glucose or other carbohydrate is important until surgical relief can be effected. Such cases are rare. The commoner form of hypoglycemia has already been described, as exaggerated response to the ingestion of concentrated carbohydrate food. These attacks can be prevented by the use of diets which provide only moderate amounts of sugar and starch per meal; totals of 20 to 40 Gm. have been found satisfactory. The absorption of the sugar may be delayed to aid the process of maintaining a normal blood sugar concentration. This is accomplished by including in each meal fat foods such as cream, butter, salad oils and meat fats. If symptoms of hypoglycemia recur despite such restrictions they may be relieved by the use of any form of sugar. Confections are not recommended, because of the common tendency to overeat and reproduce the same symptoms an hour or two later. Simple, unflavored sugar lacks the tempting power to over-indulgence. The fresh fruits are excellent sources of smaller amounts of sugar for such a purpose.

Obesity calls for a restriction of carbohydrate foods in every menu planned for weight reduction. The obvious plan of reduction is to compel the body to consume its excess of depot fat. Restriction of food fat is the first step thought of. This must not be pressed too far for reasons presented in Chapter XVI. The restriction of carbohydrate is usually more

urgent because the diets used by most obese persons are found to contain too many cereal products, potatoes and preformed pure sugars. Since most types of bread contain over 50 per cent carbohydrate, cakes about 60 per cent and ready-to-eat cereals from 65 to 90 per cent, whereas potatoes provide only about 20 per cent starch, it can be seen that restriction of cereal foods is of more importance than that of potatoes, which most people think of first. The greater satiety value of fruits and vegetables together with their content of roughage and of vitamins and minerals makes it important to retain them as sources of much of the carbohydrate in the diets for the obese. Fortunately most fruits and vegetables are relatively low in carbohydrate content. The details of recommended reduction régimes are discussed in Chapter XVII, "Weight Control."

Chapter XVI

FAT

The Needs

1. Why do we require fats? For many years fats have been recognized as the most concentrated of our energy-producing foods. The yield is 9 calories per Gm. fat as contrasted with 4 calories per Gm. of either protein or carbohydrate. A further factor is the low water content of most fat foods as compared with that of meats, eggs, milk, vegetables and fruits, which contain 60-95 per cent of water. For an individual who requires a large number of calories, the liberal use of fat reduces the bulk of food which the gastro-intestinal tract must handle. If transportation of food is a limiting factor in the choice of a diet, a high proportion of fat reduces the weight and bulk to be carried.

The presence of even a moderate amount of fat in a meal tends to slow down evacuation of the stomach, and thus the period of absorption after a meal is prolonged. Under certain circumstances this may be a disadvantage, and such clinical conditions have often been emphasized. The speed with which food leaves the stomach has been used as a criterion for judging digestibility of foods and efficiency of the stomach. Rapid digestion and early emptying have been thought desirable under all conditions. On the

contrary, prolonged stay in the stomach may be advantageous in relieving hunger, increasing the satiety value of small meals, extending the absorption of sugar over several hours or reducing excessive intestinal motility. These positive advantages of fat foods may be capitalized more frequently than many clinicians have realized.

The scientific study of nutrition in the past century has proved what practical animal husbandrymen knew long before: carbohydrate is transformed to fat by the animal body. When the possibility of synthesis of both soft and hard fats by this method had been demonstrated, it was thought that fat was a convenient but not an indispensable food. Feeding of animals on purified protein and carbohydrate foods satisfied the requirements for essential amino-acids for growth and provided enough calories. But the animals suffered effects which have come to be understood as due to deficiencies of vitamins. The first of these necessary nutrients identified in fats was fat-soluble A. Later another vitamin was found in fats, and named D. Several forms of this vitamin are now recognized. Still more recently vitamin E, alpha tocopherol, has been found in specific fats, best known of which is wheat germ oil. No one of these three vitamins is chemically classified as a fat, but their solubilities make them occur in the fat parts of certain of our natural foods. It would be possible to use solutions of these vitamins without any fat to fortify a fat-free diet adequately, but such diets would be so expensive that they cannot be considered for maintenance. Con-

centrated preparations of these vitamins may be used to augment the intake in diets in which fat must be restricted or to replenish the vitamin stores rapidly when undernutrition is discovered in the clinic.

Fats are also indispensable for good nutrition because of the requirement for some preformed highly unsaturated fatty acids. Such acids as linolenic acid contain in the long chain of carbon atoms double bonds, where there is a capacity to combine with more hydrogen, hence the name "unsaturated." These acids give the fats such low melting points that they remain liquid at ordinary temperatures. Unless the food fats contain at least a small amount of these unsaturated fatty acids there are deficiency states in animals fed on purified diets. It is assumed, but not yet proved, that the human dietary must include some of these unsaturated fatty acids. The most effective acids are linoleic, linolenic, and arachidonic, and they are found in significantly large amounts in soy bean and corn oils.

In addition to these benefits conferred by fats, some of the group, such as butter fat, olive oil and properly heated meat fat contribute desirable flavors to the diet. As in the cases of either protein or carbohydrate, fat in the diet satisfies nutritional needs and esthetic desires and aids in securing comfort in the digestive tract.

2. When do we require fats? The digestion, absorption and final oxidation of fats seem to occur more slowly than do the analogous processes for protein or carbohydrate. The insolubility in water and

the need for special chemical and biologic methods to transport fat about the body, especially through cell membranes, are involved in this low speed. Consequently fat is not depended on for quick liberation of energy. The body carries such large stores of fat, widely distributed, that a period of weeks or months of starvation is required to remove the fats from these depots. The existence of such storage of fat makes it unnecessary to provide fat in every meal or even in the diet of each day. If there is any adequate reason to exclude fat or reduce the amount of it in the diet for a few days, the only nutritional hazard induced is the consumption of some of the stored fat. This can be replaced readily enough when the fat or the calorie content of the diet is restored to a maintenance level. Fat intake is important, therefore, in terms of the average daily consumption, not the amount used on any one day.

It may be important to reduce the fat content of a meal when for any reason nausea or emesis are occurring. Under these conditions it is preferable to use foods which will be quickly digested and pass the pylorus. When liver or gallbladder disease are complicated by absence of bile from the intestine, fat should be fed sparingly, because its digestion and absorption are very slow. When prompt reduction of weight is being undertaken, the dietary fat is restricted. Under almost any other circumstances it is wise to include a fair fat ration in each meal. The amount per meal may vary without regard to the nutritional demands but should be such as will be

eaten with relish and digested with comfort. The healthy digestive tract tolerates as much as 100 Gm. fat in a single mixed meal with no difficulty.

3. What kinds of fat are required? Although the visible fatty tissues in meat and salad oils are entirely acceptable as sources of calories, these fats contain very little of vitamins A or D. They are not good sources of E or of the essential unsaturated fatty acids. Butter fat and the fats in egg yolk are especially developed sources of nutrition for the young, and contain noteworthy amounts of vitamins A and D. The oils in the germinal portions of whole cereal grains contain generous amounts of vitamins A and E. The distribution of unsaturated fatty acids of the linoleic acid type and of vitamin E in a variety of common foods probably makes it unnecessary that we select our food fats to emphasize the intake of these indispensable dietary factors. The supply of A and D is not as easily available in the low cost and most commonly used foods in America. For this reason it is important to emphasize the use of dairy products and eggs. Even with this precaution it may be important to add more vitamin D, particularly in diets for children. The fortification of foods for this purpose has been discussed in Chapter IX, "Vitamin D." Whenever the fat content of the diet is restricted to levels as low as 50 Gm. daily, most of this fat should be obtained from milk and eggs.

4. How much fat is required? The fundamental answer to this question cannot be given until the individual's calorie need is known and the protein and

carbohydrate intake have been decided on. The cal-
ories not provided by protein and carbohydrate are to
be supplied by fat. The minimum needs for these
two foods have been discussed. The minimum for
fat is not known because it depends on vitamin and
unsaturated fatty acid content, and the variations of
vitamins A, D and the acids do not run parallel. Clin-
icians believe that the safe minimum varies between
25 and 50 Gm. fat daily. The tendency is to make
larger allowances for safety. Even in reducing diets
or the feeding of patients with jaundice it is recom-
mended that the fat content should not be reduced
below 50 Gm. daily unless vitamin concentrates are
used to augment the intake of vitamins A and D.

The upper limit of fat tolerance is high. The origin
of the ketone bodies from the oxidation process of
fatty acids has led to caution in allowing too much fat
to be metabolized per day. In this connection it
must be recalled that ketosis will occur whether the
fat is fed on the day in question or is derived on that
day from tissue and depot fat which was produced
from diets previously eaten. As a consequence of this
understanding, it is recognized that the way to prevent
ketosis is to keep fat metabolism low enough so that
the capacity of the tissues to destroy acetoacetic acid
is not exceeded. In practical terms, this means merely
that enough protein and carbohydrate must be metab-
olized so that not too much fat will be used for this
purpose. The amount of carbohydrate required is sel-
dom over 100 Gm. per day, and may be as low as 50
Gm. Since protein metabolism furnishes some glu-

cose and protein oxidation produces some calories, a high level of protein intake tends also to reduce fat metabolism and thereby to prevent ketosis. The avoidance of ketosis bears no direct relation to the amount of fat fed but is accomplished by feeding adequate amounts of protein and, especially, of carbohydrate. The fat intake is to be set by the calorie demands after these other factors have been decided on.

A few individuals have unduly frequent evacuation of the bowel when using a very high fat diet, especially if the fat is chiefly butter fat. This is probably due to the stimulating action of the fatty acids of small molecular weight which are slightly soluble in water. Such individuals may have to limit the intake of butter fat moderately. As much as 100 Gm. daily does not have this type of effect.

Sources

Common sources of dietary fat are meats, eggs, dairy products, nuts, salad oils and the shortening added to pastries. The fat content of meats varies widely, and the amount left is affected so much by the type of cooking that no general statement can be made about the proportion of fat which meats furnish. Eggs are 10 per cent fat, but this is in the yolk, of which 33 per cent is fat. Milk contains about 4 per cent of fat; cream may be separated so as to contain 20-40 per cent of fat. Butter has 85 per cent fat, the remainder being water and a little salt. Cheeses vary from 20 to 40 per cent in fat, with several exceptions of the cottage cheese type which include very little

butter fat. Among the many types of nuts, only chestnuts are low in fat, whereas the other commonly used nuts contain 40-70 per cent of oils.

Special attention must be given avocados, olives and soy beans. The amount of fat which can be introduced into the diet by use of these interesting foods has been more widely appreciated in recent years. Tables of food composition must be consulted for the fat content of these plant materials in the different forms in which they are used.

Noncaloric Functions of Dietary Fat

As mentioned earlier in this discussion, certain fatty acids have come to be regarded as "essential" because of the effects observed in experimental animals when they are omitted from the diet. Rats fed diets deficient in fat develop scaly skin lesions, caudal necrosis, renal lesions and hematuria, and growth becomes retarded. Males become sterile and females produce poor litters and fail to lactate properly. The deficiency state so produced is fatal. Of the three unsaturated fatty acids extensively studied, linoleic, linolenic and arachidonic, only the first may be considered strictly essential.

Attempts to apply these observations to the clinical management of human skin disorders have met with indifferent success. Hansen[1] and his co-workers reported excellent results in the management of infantile eczema with corn oil or lard. They found a significant, measurable reduction of blood content of unsaturated fatty acids which was restored toward normal by

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[1] Hansen, A. E.: Am. J. Dis. Child., 53:933, 1937.

proper dietary measures. In adults some success has also been claimed,[2] but results obtained by a great number of clinical investigators have been disappointing. Nevertheless, there seems little doubt from evidence derived from dietary surveys that many people eat very small, and probably deficient, amounts of unsaturated fats. The subject is not yet closed. It has been reviewed by Burr and Barnes.[3]

Rancidity of fat, owing to its oxidation, produces a well recognized destructive effect on a variety of dietary factors, including vitamins A and E and certain members of the B complex. Production of deficiency states in experimental animals is possible by the inclusion of oxidized fat, and there is reason to believe that this may be important in practical human nutrition through the inadvertent inclusion of rancid fats in the diet or through oxidation in the intestinal tract. Little or no investigation of this point has been done in human subjects, and further study is badly needed to provide a guide to improvement of nutrition.

Butter fat is useful because of the color and taste contributed to the diet, the aroma which gives it distinctive flavor and the low melting point and solubility in water of some of its fatty acids, which enhance its digestibility. In addition, it carries much vitamin A and some D. It is therefore looked on by nutrition workers as the choicest of food fats. It is to be preferred as the principal fat when the total fat con-

[2] Finnerud, C. W.; Kesler, R. L., and Wiese, H. F.: Arch. Dermat. & Syph., 44:849, 1941.

[3] Burr, G. O., and Barnes, R. H.: Physiol. Rev., 23:256, 1943.

tent of the diet is greatly restricted. When diets must be liquid or soft, butter fat is most useful because it can so readily be emulsified and incorporated in palatable drinks or semisolids such as custards or whipped cream.

For economic reasons there has been a wide interest in the use of oleomargarines as butter substitutes. Originally there were numerous differences between the nutritional values of these two prepared food fats. Modern applied research has enabled manufacturers to introduce into oleomargarine not only the color, flavor and consistency of butter but also the vitamins A and D and the important unsaturated fatty acids which are among the peculiar advantages of butter as a food. Modern oleomargarines are therefore far more satisfactory competitors of butter than was the case even a decade ago. No sudden appearance of harm is to be anticipated from the introduction of even a large amount of such butter substitutes into the diet of either adults or children, and, generally speaking, oleomargarine may be considered a completely satisfactory substitute for butter. The following conclusions of the Food and Nutrition Board may be quoted: "The present available scientific evidence indicates that when fortified margarine is used in place of butter as a source of fat in a mixed diet, no nutritional differences can be observed. Although important differences can be demonstrated between different fats in special experimental diets, these differences are unimportant when a customary mixed diet is used. The above statement can only be made in respect to fortified margarine

and it should be emphasized that all margarine should be fortified."[4]

In 1941 the Federal Food and Drug Administration adopted a standard for oleomargarine to provide that the total of all emulsified addition products should not exceed 0.5 per cent of the weight of the finished product, that the total fat content must not be less than 80 per cent, that the vitamin A content should be set at a minimum of 9,000 U.S.P. units per pound (to correspond to the average content of butter) and that sodium benzoate preservative should not exceed 0.1 per cent. I believe that if these standards are met margarine may be recommended without qualification for unlimited human consumption.

Olive oil is used for its flavor in many combinations. It may be fed unmixed with other foods, but usually this is done for a druglike action. Olive oil, like egg yolk and butter fat, when placed in the duodenum stimulates the contraction of the gallbladder, and this makes the inclusion of these fats in diets advisable for patients with cholecystitis if jaundice is not marked. It has frequently been said that the diet for patients with gallbladder disease should be low in fat. On the contrary, these individuals often do well on menus which include large amounts of butter, egg and olive fats if the irritating raw vegetables, condiments and pastries are avoided. Foods fried in fat need to be omitted from such diets because of frequent intestinal irritation.

[4] A Report on Margarine, National Research Council Circular no. 118, 1943.

The fish liver oils are of tremendous value for the fortification of diets when there are deficiencies in fat-soluble vitamins A and D. They are not used in sufficiently large doses to be significant as sources of calories. Their inclusion, whether on prescription or as a routine feature of the diet, has been discussed in special chapters.

Parenteral Use of Fats

There is rarely a need for injection of fat or oil into the circulation as a food. The existence of large stores of fat in the depots and in many tissues makes it unnecessary to inject fats during periods of days or weeks when no food can be taken. The few experiments which have been undertaken in this field are of no general clinical significance. The difficulty is that the fat particles cannot be finely enough divided to permit injection of fat emulsions without danger of embolic obstruction in the capillaries. Since both carbohydrate and protein preparations are now available for parenteral use, efforts have been intensified to produce fat emulsions that will be satisfactory for this purpose. Thus far, these attempts have not been successful.

WEIGHT CONTROL

Ordinary observation elaborated into anthropometric study indicates that some persons are slender and others stout as compared with the average of the population. It would be foolish to expect that there is any single "proper" weight for a given stature, regardless of the diameters of the chest and abdomen, the size of the bones and the type of musculature characteristic of the individual. Consequently the tabulated data of height-weight-age-sex relations are always to be used with a leeway of about 10 per cent when the optimum weight for an individual is being sought. This allowance must be kept in mind when referring to any of the standard tables. Those prepared by the late Dr. Charles R. Bardeen are shown in Tables 14, 15 and 16.

One of the potent forces operating on the will to undertake control of weight is the esthetic standard of an appropriate figure. The physician may well make use of this urge, but he must be alert to prevent excessive enthusiasm from causing too rapid or excessive loss of weight. It is important to recognize that there are slender types and plump types and that no reasonable amount of effort will change the inherent body proportions of such persons. Of course, this should not be an excuse for undernutrition or for

TABLE 14.—Weights of Boys and Men in Pounds

Height, In.	Age, Yr.									
	13	14	15	16	17	18	20	30	40	50
76	...	...	...	...	...	169	179	193	201	206
75	...	...	...	158	161	164	174	187	195	200
74	...	...	153	154	156	160	169	181	189	193
73	...	...	148	149	152	155	165	175	183	187
72	...	140	142	144	147	151	160	170	178	181
71	...	135	138	140	143	147	156	165	172	176
70	...	131	134	135	139	142	151	160	167	170
69	119	126	129	131	135	138	147	155	162	165
68	115	122	125	127	131	134	143	150	157	160
67	111	118	120	123	127	130	138	146	152	155
66	107	114	116	119	123	127	135	141	147	150
65	103	109	112	115	119	123	131	137	143	146
64	100	105	109	112	115	119	127	133	138	141
63	96	102	105	107	112	116	124	129	134	137
62	93	98	101	103	108	112	120	126	131	133
61	90	94	97	100	104	109	116	123	127	129
60	86	90	94	96	101	105	113	119	124	126
59	83	86	90	93	...	...	...	...	...	...
58	80	83	87	...	...	...	...	...	...	...
57	78	80	83	...	...	...	...	...	...	...
56	74	77	...	...	...	...	...	...	...	...
55	71	73	...	...	...	...	...	...	...	...

TABLE 15.—Weights of Girls and Women in Pounds

Height, In.	Age, Yr.									
	12	13	14	15	16	17	18-19	20	30	50
71	...	...	...	...	139	142	146	150	158	174
70	...	...	...	...	136	139	142	145	154	169
69	...	...	...	131	132	135	138	142	150	165
68	...	...	125	127	128	132	135	138	142	155
67	107	114	120	123	124	128	132	134	142	155
66	104	110	116	119	121	125	129	131	138	151
65	100	106	112	115	118	122	126	127	134	147
64	97	102	108	111	114	119	122	124	131	143
63	93	99	104	107	111	116	119	121	128	139
62	90	95	100	104	108	112	117	118	124	135
61	87	92	96	100	105	110	114	115	121	131
60	84	88	92	97	102	107	111	112	118	128
59	81	85	89	93	99	104	108	110	116	125
58	78	82	85	90	96	101	105	107	113	122
57	75	78	82	87	93	99	103	105	111	119
56	72	75	78	84	90	96	100	102	109	117
55	70	72	75	81	87	94	98	100	107	114
54	67	69	72	78	84	91	...	...	...	...
53	64	66	69	75	82	...	...	...	...	...
52	61	63	66	72	79	...	...	...	...	...
51	59	61	63	69	77	...	...	...	...	...

TABLE 16.—Height-Weight-Age Table for Children

Typical Age, Yr.		Height In.	Typical Nude Wt., Lb.	
Boys	Girls		Boys	Girls
14		60	90.3	91.2
	13¼	59	85.9	85.7
13¼		58	81.0	80.0
		57	76.6	76.1
12¼	12	56	72.5	72.0
		55	68.9	68.2
11¼	11¼	54	65.4	64.7
		53	62.2	61.6
10	10¼	52	59.5	58.6
		51	56.8	56.0
9	9¼	50	54.4	53.5
		49	52.0	51.2
8	8¼	48	49.9	49.1
		47	47.9	47.0
7	7¼	46	46.0	45.0
		45	44.2	43.5
6	6¼	44	42.5	41.7
		43	40.9	40.1
5	5¼	42	39.3	38.5
4½		41	37.8	36.9
		40	36.3	35.5
	4	39	34.8	34.0
3½		38	33.3	32.6
		37	31.9	31.2
	3	36	30.5	29.8
2½		35	29.0	28.4
		34	27.6	27.0
2	2	33	26.2	25.7

neglect of frank obesity. It may be necessary to impress on the patient the clinical disadvantages of either extreme. When physician and patient agree that an attempt to alter weight is in order, detailed dietary advice is usually required. As in all medical practice, a search for etiology of the condition should precede prescription of the therapeutic program.

Aids for the Underweight

In addition to the obvious causes of undernutrition, there are numerous factors which may lead to per-

sistent weight below the accepted normal average. In clinical examination one must look for such items as (1) unusual amounts of exercise, (2) persistent emotional tension states, (3) low grade thyrotoxicosis with few physical signs, (4) anorexia, from a variety of causes, including the baffling anorexia nervosa sometimes found in young women, (5) inadequate sleep, (6) excesses of stimulants such as tobacco and caffeine, and (7) a variety of phobias and other psychotic states which involve attitudes toward food or weight standards. The diagnosis of any of these states will suggest at once the therapeutic plans which need to be introduced. The fundamental dietary approach to any of these conditions is of a single type, to be presented later. It need only be mentioned that clinical examination must be thorough enough to exclude chronic infections, malignancy, diabetes mellitus, thyroid disorders and adrenal insufficiency.

A third group of important factors which prevent gain of weight are the disorders of the digestive tract, ranging from inadequate dental equipment and oral infections to enzyme insufficiency and hyperperistalsis. Investigation of the digestive functions involves physical examination, tests for gastric acid production and visualization of the entire tract by the use of opaque mediums and x-rays. In a few clinics, special studies are made of enzyme production by stomach, pancreas and intestine. At present these are not available or dependable for the general practitioner. The oral use of enzyme preparations is seldom helpful. Apparently enzyme deficiencies are uncommon.

Achlorhydria is found in probably one tenth of the population, and the use of hydrochloric acid is beneficial to many of these individuals. If there are no symptoms referable to the digestive tract, hydrochloric acid may still be advised as a means tending to prevent anemia. The commonest type of digestive tract disorder found in underweight patients is the spastic, irritable and overactive bowel. Successful management of such a condition is well worth the effort.

The first step in treating a spastic bowel is to reduce the sources of irritation. Among foods, the common stimulants which need to be eliminated from the diet are raw fruits (except citrous fruit juices), raw vegetables, spices and condiments, nuts, fried foods and rich baked foods. Seeds, skins and obviously coarse vegetable fibers are usually forbidden. It seems probable that the cooking of fruits and vegetables does more than merely soften these structures. The cooking probably changes chemically stimulating (i.e., irritating) compounds to less effective stimulants. With such a general list of food prohibitions to begin with, each patient should be encouraged to add to the menu one article at a time until he finds how great a variety he can use without return of hyperactivity. As further aids to reduce irritability of the digestive tract, the physician may well explain to the patient the problem, the mechanism involved in the overactivity, the way in which emotional states may exaggerate the trouble and the significance of the abdominal pains which are frequent accompaniments of this syndrome. If these

means are inadequate to maintain comfortable control of the bowel, the use of belladonna is indicated, the dose to be just below that which will produce mydriasis or dryness of the mouth. As temporary aids, one may use bromide or barbiturate sedation, but it is unwise to give these drugs as routine and continuously. For lifelong difficulties, such as the spastic bowel, dieto-therapy and simple psychotherapy are preferable to the use of any drug. The possibility of an allergic basis for gastro-intestinal hyperirritability must not be forgotten.

The diets used by anyone who hopes to gain weight should be high in calorie-rich foods. Fruits may be chosen from those with 15 per cent or more of carbo-hydrate and eaten with heavy cream or whipped cream. Breakfast cereals of the ready-to-eat type are highly concentrated sources of carbohydrate, and they may be eaten with sugar and heavy cream. Bread of any type (50-55 per cent starch) spread with butter and a sweet adds further to a meal of high calorie value and low bulk. Breakfast menus should also in-clude one or two eggs, bacon, ham or a chop if pos-sible.

The noon and evening meals may be varied to fit the circumstances of the patient but should emphasize cream soups rather than broth, generous portions of meat with visible fat included, potatoes, gravy, vege-tables with cream sauces and salads containing cheese, eggs or bananas and served with liberal amounts of dressings made from salad oils. Bread, butter and sweet spreads are encouraged. Desserts may be of

almost any type tolerated, but pastries, cakes and ice cream are to be preferred. Drinks with meals or between meals should be selected from the milk products or sweetened fruit drinks. Use of coffee, tea, carbonated beverages and distilled liquors may interfere with the gain of weight.

It is obvious that few people will be able to use all the foods mentioned at each meal. These general principles should be explained, so that selections may be made to fit taste, convenience and purse. Caution must be observed that appetite is not cloyed by too much rich food, thereby defeating the purpose of the diet. If appetite is poor, it may be helped by the use of thiamine given in pure form or as one constituent of various yeast preparations. If stimulation of the appetite does not follow in a few days, thiamine therapy need not be continued, for it will be of no benefit over a long period. Use of bitter tonics is an ancient practice, and these stomachics help some individuals to reeducate their appetites. They are contraindicated in patients with an irritable bowel, who profit more from sedative than from stimulating drugs. Probably more important than the use of vitamins or stimulants are the preparation and serving of meals in ways which will please the senses and increase the zest for eating. It may be possible to introduce more calories per meal if some of the items on the menu are crisp and juicy salads or attractive hors d'oeuvres, even when these items provide few additional calories.

"The sauce to meat is ceremony." The physician

should make it his affair to inquire into the circumstances of the meals. Rest before eating may improve both appetite and digestion. Pleasant surroundings, cheerful companionship and the avoidance of conversational topics which maintain tensions common to the ordinary life of the individual are goals to be striven for. Leisure is especially to be advised. As means to these ends of avoiding tension and unpleasant situations, the cocktail hour has seemed an easy solution to many. Consumption of large amounts of distilled liquors must be avoided by those who have gastric difficulties or irritable bowels. If alcoholic drinks are desired by those who are trying to gain weight, the malt liquors with low alcohol content but as much carbohydrate as alcohol are more helpful. The appetizing effect, for those who enjoy the taste, and the vitamin B content of these drinks may also assist.

Finally, the "constitutional" factor in body contour deserves some mention. This is rather a vague concept, but it may manifest itself in an effect on the energy balance of the individual which is often far from obvious. The constitutionally thin subject is very likely to be extravagant in the expenditure of energy throughout the entire range of physical and mental activities. Much waste motion may be involved in the accomplishment of even trivial procedures which are performed by other people much more economically. Since it is manifestly impossible to alter the constitutional type of a patient, the next best expedient may be employed, that of advising against types of employment and

modes of life involving tensions and irritations and encouraging rest and relaxation. Even with minor success in this aspect of the problem, however, it is often difficult or impossible to increase energy intake over output sufficiently to effect a permanent and stable gain in weight.

Removing Excess Weight

It is commonplace that too little exercise and too much food will lead to increasing weight. The physician may have to inquire in great detail before he detects the excessive food intake. The popularity of newspaper and radio advice to the obese in the past 20 years eliminates most of this type of obesity from the physician's practice. He must remain alert to its existence, especially in a period such as the present when so many people desire to attribute obesity (and other difficulties) to "the glands." Among other causes for excess weight are: (1) unwise choices of food, (2) exaggerated hunger, (3) recurrence of hunger at short intervals after meals, and (4) a series of congenital tendencies, endocrine disturbances and hypothalamic syndromes which impose a tendency to obesity despite the consumption of an ordinary amount of food and exercise. The first three will usually respond quickly and easily to dietary limitations alone. The last group of persistent tendencies to obesity can be kept under control, but often this is accomplished only after discouragingly slow reduction. It is particularly in this latter group that the use of thyroid has become so common. Occasionally hypothyroidism is a

cause of obesity, but it may also be found in persons with normal or subnormal weight. Except in those with genuinely low basal metabolic rates, the prescription of thyroid as a reducing agent is surprisingly ineffective. Nevertheless a number of proprietary reducing medications containing thyroid are sold to the public in large amounts annually.

The diagnostic and therapeutic problems of endocrine diseases associated with obesity are not included here but should be approached without regard to the obesity, as described in texts on endocrinology. Relief from obesity for these endocrine patients is secured by dietary restrictions as outlined later for any other obese patient. The occurrence of vigorous hunger which appears one to three hours after a meal is perhaps of endocrine origin, conditioned by overproduction of insulin. The physiologic processes involved have been discussed in Chapter XV, "Carbohydrate." The only special attention necessary in reduction programs for these patients is the avoidance of large amounts of carbohydrate at any one meal and the use of small amounts between meals at the first sign of recurrent hunger, to prevent excessive desire for food. For patients who complain of great hunger or enormous appetites, patience in reeducating the digestive tract must be enjoined. Occasionally exaggerated hunger is the only prominent symptom which occurs in persons with peptic ulcer, slightly irritable bowel or diabetes mellitus. Only clinical study will reveal the nature of the problem.

METABOLISM IN OBESITY

Although there are many causes of obesity, there is one fundamental thread of continuity that applies to all types. This common factor is the intake of energy, in the form of food, which constantly exceeds the output of energy. In an extensive series of detailed and comprehensive investigations of metabolism in obesity, well reviewed by Newburgh[1] and Conn,[2] it is clear that the obese individual actually produces more heat than normal in the basal state and expends more energy to perform a measured amount of work. Because of these considerations, such subjects must consume more food to avoid weight loss. The biologic machine, regardless of any modifying circumstances, must be regarded so far as its energy aspects are concerned as no different than any other type of machine, and the laws of thermodynamics are equally applicable. The first law of thermodynamics states that whereas energy may be transformed from one form to another, it can never be created or destroyed. Applying this dictum to the problem of obesity, it is obvious that in the over-all metabolic balance sheet every calorie of energy must be accounted for. If, therefore, the obese individual reduces his food intake sufficiently to produce a negative balance over an extended period, he *must* lose weight. There are no known exceptions to this general rule. Thus, the problem in the management of obesity is to make such a negative energy balance practically possible and acceptable to the patient for prolonged

[1] Newburgh, L. H.: Physiol. Rev., 24:18, 1944.
[2] Conn, J. W.: Physiol. Rev., 24:31, 1944.

periods of time. Such a diet must necessarily contain all of the dietary essentials and be deficient only in calories.

REDUCING DIETS[3]

The essence of the wise reducing diet is that ordinary amounts of protein are used but the fat of the diet is greatly reduced. The carbohydrate intake is maintained at a level well above that which will prevent ketosis. The total food intake, in terms of calories, is well below the expenditure of energy. Under these conditions, body fat is drawn on as an important source of energy, and excess weight is used up. It makes little, if any, difference whether the body oxidizes food fat or body fat, save in the matter of weight.

The other half of the picture is the group of body functions which expend energy and therefore use up foods. There are three of major importance. First is the basal metabolism. This includes the work done in breathing and in circulating the blood when the body is at rest. It embraces all those processes which make up the continuous life of the body cells and which keep the body warm under ordinary conditions. The tonus of muscles is in the latter category. This basal metabolism is constant in the same sense that temperature and pulse rate are constant. It is under the regulation of the internal secretion of the thyroid

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[3] The following material is taken from E. L. Sevringhaus, *Endocrine Therapy in General Practice* (5th ed.; Chicago: The Year Book Publishers, Inc., 1945), chap. xiv, "Obesity."

gland. A second outlet for energy is the stimulation of heat production by foods, called specific dynamic action. This usually amounts to not more than 10 per cent of the basal metabolism. To increase this heat loss, one must increase the food. The means would therefore defeat the purpose. The third outlet for energy is physical exercise. The actual energy loss may easily go to twice the basal metabolism by exercise that is not beyond anyone. It may be only 20 per cent more than the basal metabolism. The variability of this factor is of great importance for reducing excess weight. The essence of reducing is therefore to eat less and exercise more. Some schemes have measured food intake, some exercise, and the best schemes both.

The success which will be attained in reducing excess weight is in proportion to the accuracy with which the patient will obey instructions. Definiteness of prescription is important. Therefore the physician must write a diet prescription calling for a certain amount of calories daily, to be secured from a measured amount of protein, carbohydrate and fat. This is much like the handling of diabetes, except that the leeway given the patient for variation is greater.

The great majority of patients can be reduced satisfactorily by the use of a 1,200 calorie diet. This daily total allows of plenty of bulk to satisfy hunger, plenty of protein for maintenance (at least 50 Gm.), plenty of carbohydrate to avoid ketosis (about 125 Gm.) and adequate amounts of minerals and vitamins. The diet can be made appetizing. With a diet at this

level, planned by a dietitian who appreciates tastes as well as food values, patients are often surprised at the amounts of food they may eat.

For patients whose optimum weight is over 150 lb., it may be wiser to use a 1,500 calorie diet with 75 Gm. protein. Such a diet is preferable for rapidly growing children and for pregnant women. Some patients have stubborn obesity despite honest and intelligent endeavor to follow the diet. This is particularly a problem when exercise is limited. For such patients, a diet of about 900 calories is useful. The reducing diets given here include some of the menus of the type used for these conditions. It will be noted that variety is easily achieved and that no weighing of foods is necessary.

Patients should be warned that weight reduction does not always proceed at a steady pace. Sometimes as fat is consumed from the body stores, water is stored in approximately equal amounts. If a daily weight chart is kept, no loss may be seen for as much as two weeks. But ultimately the loss of water will follow, and weight loss will be as demanded by the laws of conservation of matter and energy. It is wise to explain this to patients and also to caution against daily weighing lest discouragement come too easily.

EXPLANATIONS FOR PATIENTS ON REDUCING DIETS

Less food is furnished by the suggested diets than the individual needs for maintenance, so that excessive body fat will be utilized. To make this procedure

safe for health, it is necessary that the foods listed be eaten in the portions given. Diets are provided for different types of individuals; use only the one directed. An alternate menu for the 1,200 calorie diet is included for the use of those who must economize. Substitution of more milk and potato for fruits and part of the meat leaves the diet safe for continued use.

Variety is secured by choosing on different days the various vegetables and fruits. When "three portions" of vegetables are mentioned, it is understood that all three portions may be taken of any one vegetable; if two or three vegetables are available, one portion may be served from each, to increase the variety. Vegetables should be served without cream sauce or butter other than that listed in the diet.

Fruits should be fresh or those which are canned without sugar. No sugar should be added to fresh fruits in cooking them.

Vegetables and fruits may be taken as salads if desired. Vinegar or salad dressing made with mineral oil may be used.

Buttermilk may be used instead of sweet milk if preferred. Whole wheat bread is preferable to white or rye bread; bran bread should not be used unless by special direction. The bread may be toasted if desired. Sugar-free gelatin may be used; "D-Zerta" is such a preparation. In any meal, tea, coffee, consommé or broth without fat may be used in any amount.

"Dinner" and "supper" may be reversed and served as "lunch" and "dinner" if preferred. If hunger is annoying in midmorning, afternoon or evening, part

of any one of these meals may be eaten as a lunch at this time (and, of course, subtracted from the meals for that day).

Water may be taken freely at all times, including meals, provided it is not used to refresh the appetite and thus increase the amount of food eaten. In other words, chew the food and swallow it before drinking.

Take some sort of exercise regularly each day. Walk outdoors . . . miles each day. After four days, increase the daily walk by adding . . . miles more each day until walking . . . miles each day. Increase the speed of walking gradually. Keep a record of the weight weekly.

ACCESSORY FACTORS IN WEIGHT REDUCTION

As accessory factors in a reduction diet program, it is at times important to use iron to combat mild secondary anemia. The diets reproduced here do not lead to anemia but will not furnish therapeutic amounts of iron. The supply of fat-soluble vitamins is difficult to measure or predict. In case of any doubt it would be wise to prescribe along with a diet limited in fat the use of a concentrate of vitamins A and D, of which one of the least expensive is halibut liver oil. The calorie value of the oil can be ignored for this purpose. The water-soluble vitamins are probably furnished in adequate amounts by the diets. They may of course be added if there is a therapeutic problem in addition to obesity or if there is any reason to question the adequacy of water-soluble vitamin content of the diet.

Patients often need to be warned about the nostrums for obesity too easily available in retail drug stores. Some of these are inert. Others are known to contain unstandardized amounts of thyroid, which is obviously unwise. A significant group contains saline purgatives. These will interfere with food absorption but may lead to the cathartic habit or other damage to the intestinal tract. The use of bath salts, if effective in changing weight, does so by elimination of water through the skin. This is so obviously a temporary expedient that its futility should be apparent. Some reducing nostrums have been shown to contain the encysted ova of tapeworms, which would serve to achieve reduction by producing parasitism.

Use of special exercises to reduce weight at specified regions is at best a questionable procedure. The major problem with exercise is to increase the total output of energy at the expense of the excess body fat. We are still in ignorance of the factors controlling the localization of fat deposits in some types of obesity in which deposits about abdomen and thighs are unsightly and disabling.

MENUS FOR REDUCING DIETS

PROTEIN 50 GM., CARBOHYDRATE 126 GM., FAT 55 GM., CALORIES 1,200

STANDARD

Breakfast:
Fruit ....1 portion
Bread ....1 slice
  or
Cooked cereal ....¾ cup
Sugar ....1 teaspoon
Butter ....1 pat
Egg 1
Milk (whole)...½ cup

LOW COST DIET

Breakfast:
Bread ....1 slice
  or
Cooked cereal....¾ cup
Sugar ....1 teaspoon
Butter ....1 pat
Egg 1
Milk (whole)....½ cup

MENUS FOR REDUCING DIETS—(*Continued*)

PROTEIN 50 GM., CARBOHYDRATE 126 GM., FAT 55 GM., CALORIES 1,200

Dinner:

```
Lean meat .......1 sm. serving
Potato ..........1 portion
Vegetables .....3 portions
Bread ...........1 slice
Butter ..........1 pat
Fruit ...........1 portion
```

Supper:

```
Lean meat .......1 sm. serving
Vegetables .....3 portions
Bread ...........1 slice
Butter ..........1 pat
Fruit ...........1 portion
Milk (whole) ...½ cup
```

Dinner:

```
Lean meat .......1 av. serving
Potato ..........2 portions
Vegetables .....3 portions
Bread ..........1 slice
Butter ..........1 pat
```

Supper:

```
Potato ..........2 portions
Vegetables .....3 portions
Bread ..........1 slice
Butter ..........1 pat
Milk (whole)....1 cup
```

PROTEIN 50 GM., CARBOHYDRATE 70 GM., FAT 50 GM., CALORIES 930

Breakfast:

```
Fruit ............1 portion
Egg ............1
Bread ...........½ av. slice
Butter ..........1 pat
Skim milk .......½ cup
```

Lunch:

```
Lean meat .......1 sm. serving
Vegetables ......2 portions
Bread ........½ av. slice
Butter ..........½ pat
Fruit ...........½ portion
Skim milk .......½ cup
```

Dinner:

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Lean meat ......1 sm. serving
Vegetables ......2 portions
Bread ..........½ av. slice
Butter ..........½ pat
Fruit ...........1 portion
Skim milk ......1 cup
```

PROTEIN 75 GM., CARBOHYDRATE 136 GM., FAT 73 GM., CALORIES 1,500

Breakfast:

```
Fruit ............1 portion
Bread ...........1 slice
  or
Cooked cereal....¾ cup
Butter ..........1 pat
Egg ............1
Milk (whole)....½ cup
Sugar ..........1 teaspoon
```

Dinner:

```
Lean meat .......1 av. serving
Potato ..........1 portion
Vegetables ......3 portions
Bread ...........1 slice
Butter ..........1 pat
Fruit ...........1 portion
Milk (whole)....1 cup
```

Supper:

```
Lean meat ......1 av. serving
Vegetables ......3 portions
Bread ...........1 slice
Butter ..........1 pat
Fruit ............1 portion
Milk (whole)....½ cup
```

FOOD PORTIONS TO ACCOMPANY REDUCING DIETS

Vegetable Portions

Asparagus, cooked ..14-3″ tips
or ½ cup
Asparagus, fresh .... 8-6″ stalks
Beets, diced .... ¼ cup
Beet greens .... ½ cup
Broccoli .... ½ cup
Brussels sprouts 3
Cabbage, cooked .... ½ cup
Cabbage, raw .... ⅔ cup
Carrots .... ¼ cup
Cauliflower .... ⅔ cup
Celery, raw .... 5-7″ stalks
Celery, cooked ...... ⅔ cup
Celery cabbage,
cooked .... ⅔ cup
Celery cabbage, raw.1 cup
Cucumber, diced .... ⅔ cup
Dandelion greens .... ½ cup
Eggplant .... ½ cup
Kohlrabi .... 3 tbsp.
Lettuce .... ¼ sm. head
Green limas, canned.3 tbsp.
Mushrooms .... as desired
Okra, fresh .... ¼ cup
Okra, canned .... ½ cup
Onions, cooked ..... ½ cup

Onions, raw .... ¾ cup
Onions, raw—green
stick .... 12-4″
Oyster plant .... 2 tbsp.
Parsnips, boiled ..... 2 tbsp.
Peas, fresh .... 2 tbsp.
Peas, canned .... 3½ tbsp.
Radishes .... 12 medium
Rhubarb .... ⅔ cup
Romaine .... 10 leaves
Rutabaga .... 2 tbsp.
Sauerkraut .... ⅔ cup
Sauerkraut juice .... ½ cup
Spinach .... ½ cup
String beans, fresh...¼ cup
String beans, canned. ½ cup
Swiss chard .... ⅔ cup
Squash, Hubbard,
mashed .... ⅓ cup
Squash, Summer,
mashed .... ⅔ cup
Tomatoes, cooked ...½ cup
Tomatoes, fresh ..... 1 small
Tomato juice .... ½ cup
Turnips .... 3 tbsp.
Watercress .... 2 cups

Cheese Portions

American cheese .... 2 oz.
Cottage cheese, dry...½ cup
Cream cheese ...... 2 oz.

Potato

1 portion of potato is ½ small potato, a piece the size of a small egg—substitutes may be:
Red kidney beans....¼ cup
Corn, canned ...... 3 tbsp.
Fresh limas .... ⅓ cup
Boiled rice .... ⅓ cup

Meat

1 small portion of meat, weighing 2 oz. or the size of an egg, may be replaced by:
1 average serving of fish, chicken or 1 portion of cheese or 2 eggs
1 average portion of meat, weighing 3 oz. or the size of 1½ egg, may be replaced by:
1 large serving of fish, chicken or 2 portions of cheese or 3 eggs

Fruit Portions

Apple, raw ....⅔ sm. apple
Applesauce ....½ cup
Apricots ....4 halves
Banana ....⅓ medium
Blackberries, fresh...¾ cup
Blackberries, canned.¾ cup
Blueberries, fresh....½ cup
Blueberries, canned...⅓ cup
Cherries, red pitted,
 canned ....½ cup
Cherries, Royal Ann.18 cherries
Cherries, fresh red...½ cup
Cherries, fresh black.⅓ cup
Gooseberries ....⅔ cup
Grapefruit, fresh ....½ med. or
      6 sections
Grapefruit, canned...6 sections
Grapefruit juice ....½ cup
Grapes, fresh ....10 grapes
Grape juice ....⅓ cup
Loganberries, fresh..⅔ cup
Loganberries, canned.1 cup
Melon, cubed ....1 cup

Oranges ....1 small
Orange juice ....½ cup
Peach, fresh ....½ medium
Peach, canned—
 halves ....2 halves
 sliced ....⅓ cup
Pears, fresh ....½ pear
Pears, canned ....2 halves
Pineapple, fresh or
 canned, diced .....½ cup
 sliced ....1¼ slice
Pineapple juice ......½ cup
Plums, fresh or
 canned ....3 plums
Prunes, fresh or
 canned ....3 prunes
Raspberries, fresh ...1 cup
Raspberries, canned..½ cup
Strawberries, fresh...1¼ cup
Strawberries, canned.1½ cup
Tangerines ....2 medium

DENTAL PROBLEMS IN NUTRITION

Dental caries is probably the most universal human disease. The etiology remains obscure despite all efforts which have been made to relate it to infection, inadequate diet and disturbed metabolism from other causes. Attention of investigators has been directed to pyorrhea alveolaris, abnormal structure of teeth, apical infection, bleeding gums and malocclusion, all of which involve structures the integrity of which almost certainly has a direct bearing on the problem of dental caries. In none of these conditions can the pathologic process be shown to be related solely to a disturbance in nutrition. On the other hand, there is good evidence that deficiencies of various sorts may be important factors in the development of dental disease.

The teeth arise from two embryologic cell layers, namely, ectoderm and mesoderm. The enamel is derived from the former, and along with the skin and other ectodermal structures it displays a definite sensitivity to lack of vitamin A. This is especially true during the formative period of both deciduous and permanent teeth. Under these circumstances the enamel forming from within establishes an uneven, indented contour in contrast to the usual even curved surface seen in healthy teeth. In addition, the enamel

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produced by such cells is incompletely calcified, by reason of which saliva and water penetrate to abnormal depths, carrying in food material which may serve as culture medium for bacterial growth. The lines of fusion between the lobes on the occlusal surfaces of the molars may not entirely close, leaving small defects in the enamel which may harbor food particles and bacteria.

Because of the mesodermal origin of dentin which fills the pulp cavity, the need for ascorbic acid might be anticipated since this vitamin seems to play a special rôle in the function of many mesodermal structures, particularly the blood vessels. Defective dentin results from a deficiency of vitamin C, which again is probably somewhat more accentuated if it occurs during the period of development. The gingival hemorrhages which accompany these changes are well known manifestations of scurvy.

The importance of an adequate supply of vitamin D is almost self-evident, since the formation of dentin and enamel involves a calcification process closely related to bone formation and shares the factors which control it. An adequate source of calcium and phosphorus is no less necessary, but fortunately an abundant reservoir in the cancellous portions of the long bones eliminates the danger of a shortage of these elements even though the dietary intake fails. The blood serum calcium is dependent on the amount of parathyroid hormone and the serum protein level far more than on the dietary supply of calcium, since the bones contain a large supply of calcium in equilibrium

with that of the blood. It is interesting how completely the teeth resist decalcification in hyperparathyroidism in which calcium is being constantly withdrawn from the bones. In this disease generalized demineralization of the bones usually occurs, and the alveolar processes in which the teeth are embedded may be resorbed, but rarely if ever do the teeth themselves suffer any demonstrable loss of calcium salts. Other conditions calling for increased calcium and phosphorus intake, such as pregnancy and lactation, may result in demineralization of bone if these elements are not supplied, but the teeth do not appreciably participate in this process despite the common belief to the contrary. The increased incidence of dental caries during pregnancy is probably due to other, unidentified causes. Several workers have called attention to this lack of correlation between pregnancy and demineralization of teeth.[1]

Fluorine has long been known to occur in teeth in small amounts. Relationship between fluorine content of teeth and dental disease was first suggested in 1908, but most of the significant investigations have been made within the past decade. It is now clear that municipal water supplies which contain 1 or more parts per million of fluorine may cause the appearance of "mottled enamel" in individuals in the community who have consumed that water since infancy or during the period of tooth formation. In practical experience, however, mottling of dental enamel is almost invariably associated with fluorine concentrations of 3 parts per

[1] Deakins, M., and Looby, J.: Am. J. Obst. & Gynec., 46:265, 1943.

million or higher. On the other hand, a deficiency of fluorine in drinking water (below 1 part per million) is regularly associated with an increased incidence of dental caries. Thus, there is clearly an optimal range for fluorine concentration which will provide significant protection from dental caries and still not cause dental fluorosis. This range extends from 1 to 1.5 parts per million, and it has been so carefully established by a great volume of excellent observations that the chemical constitution of municipal water supplies has become a matter of the greatest importance in the field of public health. The United States Public Health Service has set up standard criteria calling for rejection of a water supply showing an excess of 1.5 parts per million of fluorine.

Fluorine concentration in drinking water varies widely under natural conditions, and the geographic distribution of dental abnormalities correlates almost perfectly. A great deal of the United States has been carefully mapped, and increasing attention is being directed to this problem throughout the world. Some water supplies have been found to contain fluoride concentrations above 10 parts per million, and the occurrence of fluorine-free water is widespread.

The exact mechanism by which fluorine deficiency leads to dental caries is unknown, but two important working hypotheses have been proposed. The first relates elemental fluorine to the production of apatite, the calcium, phosphorus, fluorine complex of dental enamel, by the developing tooth structure. In the absence of adequate amounts of this element a defective enamel

is produced which impairs tooth structure in such a manner that restoration of an adequate fluorine supply in later years cannot compensate for the deficiency during the period of tooth formation. This would explain the observed lack of benefit of optimal fluorine intake in individuals who were reared during early childhood in deficient areas and moved subsequently into a higher fluoride environment. The second theory proposes an inhibiting effect of low fluoride concentrations in saliva (probably about 0.1 part per million) on the growth of the lactic acid-producing organisms known to play a part in the development of dental caries. It is possible that both mechanisms are important in the etiology of dental disease; there is excellent evidence to support each, and further study may bring new, critical evidence to light which will help to solve this problem.

Artificial fluorination of municipal water supplies is now being studied on a wide scale. Several American cities are conducting well controlled scientific experiments which it is hoped may determine whether or not this is a legitimate and safe public health procedure. One of the most interesting is that being conducted at Kingston and Newburgh in New York State, in which the former city is to serve as a control. McClure[2] summarized the scientific background for this experiment, and Dean[3] has sounded a note of caution which is well timed and appropriate in view of the increasing interest in this matter and the pressure being applied to munic-

[2] McClure, F. J.: Pub. Health Rep., 59:1543, 1944.
[3] Dean, H. T.: J. Am. Water Works A., 35:1161, 1943.

ipal government agencies by undiscriminating, non-scientific lay groups. It is perfectly clear that there may yet be discovered one or many other environmental factors which have a bearing on dental health. Fluorine supply is one which seems to correlate perfectly, but a multitude of ramifications of the problem must be investigated before general fluorination of municipal water supplies can be recommended without qualification.

The topical application of fluoride solutions to the teeth has been proposed as one means for reducing the incidence of dental caries. In one study,[4] the use of a 2 or 3 per cent solution resulted in a reduction of 25-50 per cent in caries incidence in the youngest age groups and had little or no effect in adults. Here again, the effect may be due to a direct chemical reaction at the external surfaces of the teeth leading to the production of a caries-resistant layer of enamel, or it may act through improvement of the chemical environment of the teeth by bacterial inhibition. The efficacy of this procedure is controversial, but it deserves attention.[5]

The rôle of infection in relation to diet as a cause of dental caries is still unsettled, but some good evidence has been brought to bear on the subject. An interesting correlation has been found between the presence of acid-forming bacterial flora in the mouth, chiefly Lactobacillus acidophilus, and the occurrence of dental caries. The explanation for this fact is not

[4] Bishop, R.: Dent. Health, 5:10, 1945.
[5] Knutson, J. W., and Armstrong, W. D.: Pub. Health Rep., 60:1085, 1945.

clear, since habitual users of sour milk infrequently have these organisms in abundance in the mouth, whether they are present in the intestine or not. The underlying humoral or environmental factors favoring their growth are likewise unknown, but one is reminded of the profuse growth of Vincent's organisms in the mouths of pellagrins, with prompt clearing of the infection when the dietary insufficiency is removed. Accepting as the chief offending organism Lactobacillus acidophilus, it is apparent that its capacity to form lactic acid depends to a large extent on the availability of carbohydrate which can be fermented. Because of their easier fermentability, the purified sugars are better culture mediums for this organism than are the starches. The saliva of caries-active individuals has been shown to produce acid at a much higher rate than does that of caries-immune subjects. Various inhibitors of glycolysis will reduce this activity. Among these are fluoride, iodoacetate and synthetic vitamin K. That fluoride may have some practical significance in the etiology of dental caries has already been mentioned. Vitamin K inhibits acid production without inhibiting growth of the organisms, and its use may be made more practical as observations are extended. Two series of experiments may be cited in this connection. Burrill *et al.*[6] studied human subjects and reported a 54 per cent reduction in new carious lesions in individuals chewing vitamin K gum as compared with a 21 per cent reduction in those

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[6] Burrill, D. Y.; Calandra, J. C.; Tilden, E. B., and Fosdick, L. S.: J. Dent. Research, 24:273, 1945.

chewing plain gum. The statistical significance of these figures is questionable. On the other hand, an investigation by the Medical Department Professional Service Schools[7] shows no effect from vitamin K chewing gum under similar conditions. This is an important point to be settled, but regardless of the clinical implications, the bacteriostatic effect of vitamin K undoubtedly represents an environmental rather than a nutritional effect and probably is correlated with the quinone structure of vitamin K and its attendant chemical behavior rather than with its better known activity.

The high solubility of purified sugars might be expected to carry them away from the tooth surfaces before significant fermentation could occur, but saliva and other liquids cannot penetrate into many of the tiny cracks and other defects, particularly when food particles are blocking the way. In this manner, the proper conditions for fermentation can be produced, with the end-result that the local concentration of lactic acid rises high enough to slowly dissolve enamel or dentin. In this connection, a low incidence of dental caries has been observed in diabetics under careful management, particularly when the diet has been high in fat and low in carbohydrate. Conversely, a high incidence of caries has been reported in individuals who constantly suck on hard candies. In addition, a high intake of refined carbohydrate tends to reduce the intake of other essential nutrients, thereby giving rise to additional possible sources of trouble.

Since the destruction of a tooth involves the dissolu-

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7 Bull. U.S. Army M. Dept., 5:265, 1946.

tion not only of calcium salts but of the tooth matrix composed of protein, interest has been stimulated in the possible rôle in dental caries of proteolytic enzymes of invading bacteria. Some evidence has been produced that this mechanism has considerable practical importance,[8] but there is no reason to believe that it bears any relation, under ordinary conditions, to the dietary intake of protein.

It will be apparent from the discussions of vitamin D and minerals, Chapters IX and XII, that development and growth of the bones of the skull and jaws depend to a large degree on nutrition. The problems of orthodontia involve nutrition to this extent, and furthermore they bring into focus the importance of the physical character of the food and the necessity for exercise of the muscles of mastication and pressure on the apexes of the teeth. It is essential that there be firm food to assist in this development of muscles, alveolar processes and softer connective tissue, especially during childhood and youth. Furthermore, it is well recognized that the loss of teeth through either decay or extraction leads to faulty spacing and alinement of remaining teeth, so that the complete dental structure presents an interdependent system, the integrity of the whole depending on the health of all constituent parts.

Thus, it is impossible at present to state with any finality the relative importance of nutritional factors in the cause and cure of dental caries. It is even more

[8] Gottlieb, B., and Hinds, E. C.: J. Dent. Research, 21:317, 1942; Pincus, P.: Brit. Dent. J., 76:231, 1944; Frisbie, H. E.; Nuckolls, J., and Saunders, J. B.: J. Am. Coll. Dentists, 11:243, 1944.

impossible to relate that disease to the lack of any specific nutrient. In an interesting study on children, Boyd[9] reported almost complete success in converting caries-susceptible into caries-resistant cases by dietary means alone. The diets used were not designed to test the value of any single dietary factor, but were planned to contain the optimal nutritional needs of each individual child. The daily requirements as defined in previous chapters were met or exceeded and no vitamin supplements were given with the exception of cod liver oil for its vitamin D content. The brilliant results of this investigation give strong added emphasis to the nutritional approach to this perplexing and important problem.

The dentist must not forget that the structure and position of teeth and the character of the jaws are affected by inherited patterns and by the endocrine activity of the pituitary, parathyroid, thyroid and reproductive glands. It is thought that disturbances of pancreatic and adrenal function also leave records in tooth structure. Infectious diseases and other febrile illnesses leave marks which can be found histologically in teeth removed at a later date.

From this discussion it should be apparent that the prevention of dental disease with the coexistent amelioration of the health of the people which it entails is the combined responsibility of both the dentist and the physician. In so far as nutritional factors are concerned, the most advantageous time to begin effective prophylaxis for any individual is during the prenatal

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[9] Boyd, J. D.: Am. J. Dis. Child., 67:278, 1944.

period when the mother is supplying the materials out of which healthy teeth can be built. The protection of the pregnant woman from dental decay is thus a problem of the greatest importance, since the dental health of the child in later years is also at stake. She must be provided adequate amounts of vitamins A, C and D in particular. An abundant supply of calcium is necessary so that her own reserves may be maintained intact. Since there is no risk of overfeeding these vitamins within reasonable limits, only the minimum requirements need be considered. For vitamin A this should preferably be at least 10,000 I.U. daily, for vitamin C at least 100 mg. and for vitamin D from 1,000 to 1,200 I.U. There is no reason why these nutrients should not be obtained entirely from the diet, but supplements may always be added if necessary. For addition of calcium salts to the diet, the current use of calcium phosphate is probably one of the least satisfactory methods, owing to the relative insolubility of this particular compound in alkaline solution. It is probable that calcium lactate or gluconate, 10-30 gr. (0.6-2 Gm.) taken in water 30 minutes before meals will provide better absorption. However, there is no substitute for milk as a source of calcium. Here the calcium and phosphorus are present together, in the optimum ratio of 1.2:1, and these elements are efficiently utilized. One quart daily will adequately fill the need throughout pregnancy and lactation. Particular emphasis on the aforementioned nutrients does not imply a lack of importance of the others; further study may reveal new relationships.

Good dietary habits are no less important during childhood, adolescence and adult life, but there are no particular nutritional requirements for good teeth that have not already been discussed in previous chapters as equally applicable for good health in general.

CHAPTER XIX

THE ECONOMIC SIDE OF CLINICAL NUTRITION

Even though we do not know the full extent of the nutritional problem in the United States, as President Roosevelt has told us "every survey of nutrition, by whatever method conducted, in whatever part of the country, shows malnutrition to be widespread and serious." Studies of family diets by the Department of Agriculture in all income groups of the Nation show that one-third of our people are getting food inadequate to maintain good health. Less than one-fourth of us are getting a "good diet," even when measured by the old standards which are lower than the "gold standard" presented to us by Doctor Wilder's committee. Some people can't afford to buy the food they need; others spend their limited food budget unwisely; still others have fixed and faulty food habits. We Americans want good health to be the heritage of all, on as democratic a basis as the suffrage itself. We want no property qualification for health.[1]

The cost of food continues to be a matter of tremendous importance to most people. The high standard of living so often spoken of in the United States has led many to think that an adequate diet is easily available for most families. The period of economic depression following 1929 witnessed millions thrown onto the assistance of private or public charity for the maintenance of life. Study of the cost of feeding large groups received a further impetus. At that time it began to be realized that a supply of protein and of calories which would maintain an individual while at work was relatively cheap as compared with a diet containing enough minerals and vitamins to meet the

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[1] From the address by Surgeon General Thomas Parran, before the National Nutrition Conference, May 28, 1941. *Public Health Reports* 56:1252, June 13, 1941.

minimum standards for safety which nutrition ex-
perts urged. One illustration of this was the paradox
of indigent obese patients in the clinics, who literally
could not afford to reduce weight except by painful
starvation. This was due to the inclusion in all medi-
cally planned reduction régimes of fruit, vegetable
and dairy products rather than cereal grains and con-
centrated fats. The cereal grains and potatoes form
an inexpensive source of energy-producing food, and
hence any diet provided from a meager purse must
use the maximum of starchy foods.

An equally difficult situation has been encountered
during the food restrictions arising out of wartime
rationing and the enormous economic difficulties which
have attended postwar inflation, both with and without
regulated ceiling prices. In any attempted analysis of
the consequences of these conditions on food prices and
nutritional status of the population at large it becomes
apparent that the disproportionate rise in food prices
and family incomes has constituted the source of
trouble. Reliable information has been available on this
subject through the public press, which has assisted in-
telligent people to appraise and understand their eco-
nomic dilemma. Thus, a study of income distribution
conducted by the Federal Reserve Board and the
Bureau of Agricultural Economics was reported in the
United States News for July 26, 1946. It covered
family incomes for the year 1945 and represented data
on 45,000,000 families. According to this investiga-
tion, 47.1 per cent of American families were receiv-
ing $2,000 or less annually, and 20.1 per cent received

less than $1,000. In the face of sharply rising prices, the need for wisdom and care in the expenditure of every dollar by at least this half of American families is obvious.

Two other reports from the same journal are worth mentioning.[2] By mid-August, 1946, the average cost of food had risen about 100 per cent above its 1939 level. This rise was quite evenly distributed through all important classes of foods, but was perhaps most serious in relation to meat, poultry and dairy products. By mid-fall, 1946, an income of $4,719 was necessary for a family of four to maintain the same standard of living made possible in 1941 by an income of $3,200. This represents a rise of 47.4 per cent, which had not been paralleled by actual increases in income. Fortunately it was offset to some extent by savings accumulated during the war, but it is inevitable that some of the disparity between income and prices must be translated into a decline in quality of diets and an increase in marginal or subnutrition.

Thus it is apparent that during periods of great economic instability, such as that following World War II, the economic aspects of nutrition manifest a parallel instability. Studies of absolute food costs and percentage distribution of income expenditures at any one time are valueless because of constant and rapid fluctuations. Relative values, however, continue to be important since the "protective" foods must always be stressed and the minimum recommended standards for satisfactory nutrition must always be met.

[2] United States News, Vol. 21, Nos. 11 and 16, 1946.

There is no easy answer to the question of how to live well at low cost. An increasing popular value placed on dairy products, fruits, and vegetables has followed the publication of the results of nutrition research. Production of these food materials is increasing rapidly and their costs have decreased, but it does not seem probable that such perishable foods will soon become as cheap as the easily preserved cereals, fats and meats. The perishable fresh foods, even though preserved by the introduction of new technics for refrigeration, dehydration or canning, have an unavoidably high cost of production: Efforts to reduce all these costs are warranted.

From the point of view of the clinician attempting to improve the low cost diet, a different approach is required. The economics of adequate diets must be based not alone on calories, maintenance protein and satisfaction of hunger but also on vitamins and minerals. This adjustment is in process, as it will continue to be for an indefinite period. Intensive, planned, nation-wide effort to improve the nutrition of the people of the United States was begun in 1941. At that time, as a practical expedient, special stress was laid upon the daily intake of "protective foods," represented by milk, eggs, meat, vegetables, citrus fruits and whole grain cereals.

An important stride was taken by the U. S. Department of Agriculture, in the study reported in Farmer's Bulletin no. 1757, September, 1936, under the title DIETS TO FIT THE FAMILY INCOME, written by R. S.

Carpenter and H. K. Stiebeling.[3] It is recommended for any housewife who desires to feed a family well and economically. The costs of food are based on prices during 1935, in retail city markets. These authors checked the prices for foods in similar markets late in 1941 and found no great change in cost. However, the definite increase in the cost of living during 1942 serves to make the cost figures for these diets of little value save in showing the relative expensiveness of the different types of diet. Even in the postwar period, despite prevailing chaotic economic conditions, this Bulletin still contains much of value.

The fundamental plan of this series of dietary suggestions is the use of four typical diets called (1) liberal, (2) moderate cost, (3) minimum cost and (4) restricted. The chief difference between diets 1 and 2 is the reduced amount available for selection of foods and for relishes, whipping cream and special items. This calls for more thought and ingenuity in preparing attractive meals but does not reduce the safety of the diet as a source of all important nutrients. The difference between diets 2 and 3 is in the limited choices for variety, the reduced amount of meat and the increased emphasis (relatively) on milk and cereal foods. The fourth, or restricted, diet is offered "for emergency use only, because it may not provide a sufficient surplus of protective foods (milk, eggs, tomatoes, and green vegetables) to insure good health

[3] This bulletin may be secured at a cost of 5 cents on application to the Superintendent of Documents, Washington, D. C. The authors are grateful to Dr. Stiebeling for permission to quote from this helpful study.

over an indefinite period." Experience since the Bulletin was first published shows that the fourth, or restricted diet, is unsafe in many cases. Therefore it is no longer being suggested even for emergencies, lest it be considered a safe minimum diet. As concrete illustrations of these diets, the summaries are reproduced here.

LIBERAL DIET

MILK: One quart daily for each child (to drink or in cooked food). One pint for each adult (to drink or in cooked food).

VEGETABLES AND FRUITS: Six to seven servings per person daily.
  One serving daily of potatoes or sweet potatoes.
  One serving daily of tomatoes or citrus fruits.
  Two and one-half to three servings daily of vegetables, at least half of which are leafy, green or yellow.
  Nine to 10 servings a week of fruit (once a day, sometimes twice).

EGGS: Four to six a week; also some in cooking.

MEAT, FISH OR POULTRY: Once a day, sometimes twice.

BUTTER: At every meal.

BREAD, CEREALS AND DESSERTS: As needed to meet calorie requirements or as desired, so long as they do not displace the protective foods.

The suggestions for a moderate cost diet may also be modified up or down the scale, according to the amount of money a family can or wishes to spend for food. Increase in the amount of vegetables, fruits, eggs and meat toward the quantities suggested in the liberal diet list tends to improve vitamin, mineral and protein values and brings up the cost. A diet of this type can, on the other hand, be scaled down in cost by increasing the amount of dried beans and peas and grain products and decreasing somewhat the quantity of some of the other foods.

The cost of this diet was $13 to $15 a week for a family of four at 1941 average retail prices and well within the reach of many families in this country.

For a family of two adults, the cost was $8 to $10 a week in 1941, and for a family of seven, $20 to $25.

MODERATE COST DIET

MILK: One quart daily for each child (to drink or in cooked food).
One pint for each adult (to drink or in cooked food).

VEGETABLES AND FRUITS: Four and one-half to five servings per person daily.
One serving daily of potatoes or sweet potatoes.
One serving daily of tomatoes or citrus fruits.
One serving daily of leafy, green or yellow vegetables.
Three to five servings a week of other vegetables.
One serving daily of fruit.

EGGS: Two or three a week for adults; four or five for young children; a few in cooking.

MEAT, FISH OR POULTRY: About 5 times a week. Or daily if prepared in combination with cereals or vegetables.

A CEREAL DISH: Daily.

BREAD AND BUTTER: At every meal.

DESSERTS: Once a day, sometimes twice if desired and if it does not displace the protective foods.

MINIMUM COST DIET

MILK: One quart daily for each young child (to drink or in cooked food).
Three-fourths of a quart daily for each child over 4 (to drink or in cooked food).
One pint for each adult (to drink or in cooked food).

VEGETABLES AND FRUITS: From three to four servings per person daily.
Eight to nine servings a week of potatoes and sweet potatoes (once a day, sometimes twice).
Two or three servings a week of tomatoes (or of citrus fruits in season) for each adult and child over 4; 4-6 tablespoons of tomato juice or 2 tablespoons of orange juice daily for each child under 4.
Five to six servings a week of leafy, green or yellow vegetables.
Two to three servings a week of dried beans, peas or peanuts.
One serving daily of fruit or an additional vegetable.

EGGS: Two to three a week for adults; four or five for young children; a few in cooking.

MEAT OR FISH: Three to four times a week (more frequently if the meat dish is often a meat and cereal combination).

A CEREAL DISH: Once a day, sometimes twice.

BREAD: At every meal.

DESSERTS: About once a day if desired, such as cereal pudding, cookies, simple cakes, shortcake and inexpensive pastries and fruits.

A minimum cost diet should be modified only to

improve it. If the pocketbook allows, the food value and flavor of the suggested assortment of foods may be improved by increasing somewhat the fruits and the leafy, green and yellow vegetables. The moderate cost plan may be the guide for such changes. However, the family that can barely afford an adequate diet by making food money go as far as possible should not try to adjust the assortment of foods in the minimum cost diet. Any modifications in a restricted diet should be those that will improve its nutritive value. Families who, because of some emergency, are living on a diet which is more restricted than these plans suggest, should look forward to increasing as soon as possible the quantities of fresh succulent vegetables, fruits, milk, eggs and lean meats. These changes would, of course, improve the protein, vitamin and mineral values, but they would also increase the cost.

It is well known that most types of grade C meats are just as nutritious as the grade A cuts. The preparation of the poorer grade requires more time in cooking and more ingenuity and care in preparation for consumption, but its use will pay large dividends for families on marginal incomes. By purchasing the poorer quality and less popular cuts of meat, the housewife can maintain the quantity and nutritional value of these foods without a proportional increase in cost.

Vegetables "in season" should always be used when possible. It is less expensive to use canned vegetables than vegetables which have been shipped from distant parts of the country. The maintenance of specific

standards in the canning industry has provided the public with commercially canned vegetables as high in vitamin content as fresh, home-cooked vegetables. If a family can budget so as to allow quantity buying of food, the purchase of canned vegetables by the case is a good investment. Purchase of the crop from the preceding year just as the present year's crop is reaching the market often results in a discount.

Each summer the price of oranges and grapefruit increases noticeably for a few months. At such times it is worth while to turn to a few of the common summer vegetables which are rich in ascorbic acid. Among these are broccoli, brussels sprouts, cauliflower, collards, peppers and turnip greens. Cabbage is also a valuable source of this vitamin and is, along with carrots, one of the least expensive year-round vegetables to be found in the markets. For this reason, both should be used extensively as raw food.

According to average retail prices during 1941, the cost of the minimum cost diet, suggested above, for a family of four was $8 to $10 per week; for a family of two, $5 to $6, and for a family of seven, $14 to $17.

The Bulletin furnishes detailed suggestions for the selection of foods by groups according to nutritive values. Then a section presents a "Week of Sample Menus for Each Diet Plan." There are valuable more recent supplements to this Bulletin, issued as simple folders by the Bureau of Home Economics, U. S. Department of Agriculture, February, 1942. These are called "Market Lists for Moderate-Cost Meals" and ".... for Low-Cost Meals" and may be purchased

at $1.25 per 100 copies from the Superintendent of Documents, Washington, D. C. In simple tabular form these lists show the weekly quantities of food advised for persons of all ages from infants to adults and at different levels of activity. Specimen moderate cost and low cost weekly marketing lists are reproduced on pages 373 and 374 to indicate the advantages of providing housewives with these inexpensive aids. These materials are a part of the intensive, nation-wide effort to improve the nutrition of the citizens of the United States, begun in 1941. The sound principles of low cost buying of food on which these lists are based make their use no less valuable during a period of inflated prices than they were at the time they were originally published.

How to Use the Market Lists

1. On the blank lines at the bottom of the list, write down the name of each person who eats at your table. Put the name of one person on each line.

2. Find the line in the table that describes each person.

3. Now, beside each name you write down, fill in the quanties of foods which the table recommends for a person of that sex, age and activity.

4. When all the quantities are filled in, add up each column.

5. There you have your family's marketing list for the week.

For a family planning to produce the whole amount of any one or more of the various kinds of food needed throughout the year: multiply the quantities that the family needs for a week by 52; then add something extra (from one-fourth to one-half) for guests and for a margin of safety.

Just how much it costs to follow any diet plan depends on four things . . . family size, the general level of food prices, the food choice made within various food groups, and the skill and thrift of the person who buys the food and prepares the meals.

MARKET LIST FOR MODERATE COST MEALS

KINDS AND QUANTITIES OF FOOD FOR A WEEK

Family Members	Milk [1] (Qt.)	Potatoes, Sweet Potatoes (Lb.—Oz.)	Dry Beans, Peas, Nuts (Lb.—Oz.)	Tomatoes, Citrus Fruit (Lb.—Oz.)	Leafy, Green and Yellow Vegetables [2] (Lb.—Oz.)	Other Vegetables and Fruit [3] (Lb.—Oz.)	Eggs (No.)	Meat, Poultry, Fish [4] (Lb.—Oz.)	Flour, Cereals [5] (Lb.—Oz.)	Fats and Oils [6] (Lb.—Oz.)	Sugars, Sirups, Preserves (Lb.—Oz.)
Children											
9–12 months	6	0—14	.....	1—8	1—8	0—8	5	.....	0—12	0—1	0—1
1–3 years	7	1—2	.....	1—8	1—8	1—8	6	0—6	1—2	0—2	0—2
4–6 years	7	1—8	0—1	1—8	2—0	2—0	6	0—12	1—14	0—5	0—5
7–9 years	7	1—12	0—2	1—8	3—0	3—0	6	1—0	2—2	0—8	0—8
10–12 years	7	2—8	0—2	1—12	3—8	4—0	6	2—0	3—4	0—12	0—12
Girls											
13–15 years	7	2—10	0—3	1—12	3—8	3—4	6	2—8	3—4	1—2	0—14
16–20 years	7	2—4	0—2	2—0	3—8	4—4	6	2—8	2—8	0—12	0—12
Women											
Moderately active	5	2—10	0—3	2—0	3—8	4—0	5	2—8	2—8	1—0	1—0
Very active	5	3—2	0—4	2—0	3—0	4—0	5	3—0	3—12	1—4	1—4
Sedentary	5	1—12	0—2	2—0	3—8	3—8	5	2—8	2—2	0—12	0—12
Pregnant	7½	1—12	0—2	2—0	4—0	4—8	6	2—8	2—2	1—0	1—0
Nursing	10½	2—10	0—2	3—8	4—0	5—0	6	2—8	2—12	1—0	1—0
Boys											
13–15 years	7	3—2	0—3	2—0	3—0	5—0	6	2—12	4—8	1—2	1—2
16–20 years	7	4—0	0—4	2—0	3—0	5—8	6	3—0	5—0	1—9	1—9
Men											
Moderately active	5	3—2	0—4	2—0	3—0	4—0	6	3—0	3—12	1—4	1—4
Very active	5	5—6	0—8	2—0	3—0	5—0	6	3—12	7—0	2—1	2—1
Sedentary	5	2—10	0—3	2—0	3—8	3—4	6	2—8	2—8	1—0	1—0
Total	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....

[1] Or its equivalent in cheese, evaporated milk or dry milk. Five ounces of American (Cheddar) cheese, or 1 qt. skim milk and 1¼ oz. butter, or 3½ oz. dry skim milk and 1½ oz. butter, or 17 oz. evaporated milk are about equivalent to 1 qt. fluid whole milk.

[2] Such as green cabbage, kale, snap beans, carrots.

[3] Such as apples, bananas, peaches, onions, corn, celery.

[4] Exclude bacon and salt side.

[5] Count 1½ lb. bread as 1 lb. flour. Use chiefly whole-grain or enriched products.

[6] Include bacon and salt side.

Market List for Low Cost Meals

Kinds and Quantities of Food for a Week

Family Members	Milk [1] Qt.	Potatoes, Sweet Potatoes Lb.—Oz.	Dry Beans, Peas, Nuts Lb.—Oz.	Tomatoes, Citrus Fruit Lb.—Oz.	Leafy, Green and Yellow Vegetables [2] Lb.—Oz.	Other Vegetables and Fruit [3] Lb.—Oz.	Eggs No.	Meat, Poultry, Fish [4] Lb.—Oz.	Flour, Cereals [5] Lb.—Oz.	Fats and Oils [6] Lb.—Oz.	Sugars, Sirups, Preserves Lb.—Oz.
Children											
9–12 months	5½	1 — 0	.....	1 — 8	1 — 0	.....	5	.....	1 — 0	0 — 1	0 — 1
1–3 years	5½	1 — 8	.....	1 — 8	1 — 4	1 — 0	5	0 — 4	1 — 0	0 — 4	0 — 3
4–6 years	5	2 — 8	0 — 2	1 — 8	1 — 8	1 — 8	5	0 — 6	2 — 0	0 — 6	0 — 8
7–9 years	5	3 — 0	0 — 4	1 — 8	1 — 12	1 — 8	5	0 — 12	2 — 8	0 — 12	0 — 10
10–12 years	6	3 — 8	0 — 6	1 — 8	2 — 0	2 — 0	4	1 — 8	3 — 4	0 — 14	0 — 12
Girls											
13–15 years	6	4 — 0	0 — 8	1 — 8	2 — 8	2 — 0	5	1 — 12	3 — 8	1 — 0	1 — 0
16–20 years	6	3 — 8	0 — 8	1 — 8	2 — 8	2 — 0	5	1 — 12	2 — 12	0 — 12	0 — 12
Women											
Moderately active	4½	4 — 0	0 — 8	1 — 8	2 — 0	2 — 0	4	1 — 8	3 — 8	0 — 13	1 — 0
Very active	4½	5 — 0	0 — 12	1 — 8	2 — 4	2 — 0	3	2 — 0	4 — 4	1 — 0	1 — 4
Sedentary	4½	4 — 0	0 — 4	1 — 8	2 — 0	2 — 0	4	1 — 8	2 — 8	0 — 12	0 — 11
Pregnant	7½	3 — 0	0 — 6	2 — 0	3 — 0	2 — 0	6	1 — 12	2 — 12	0 — 12	0 — 12
Nursing	10½	5 — 0	0 — 4	3 — 8	3 — 0	3 — 0	4	1 — 8	2 — 12	0 — 15	1 — 0
Boys											
13–15 years	6½	5 — 8	0 — 8	2 — 0	2 — 8	2 — 8	4	1 — 12	4 — 8	1 — 2	1 — 0
16–20 years	6	7 — 0	0 — 12	2 — 0	2 — 8	2 — 8	3	1 — 12	6 — 0	1 — 5	1 — 4
Men											
Moderately active	4½	5 — 0	0 — 12	1 — 8	2 — 4	2 — 0	3	2 — 0	4 — 4	1 — 0	1 — 4
Very active	4½	7 — 8	1 — 0	1 — 8	2 — 8	2 — 0	3	2 — 8	9 — 4	1 — 6	1 — 12
Sedentary	4½	4 — 0	0 — 8	1 — 8	2 — 0	2 — 0	3	1 — 8	3 — 8	0 — 13	1 — 0
Total	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....

[1] Or its equivalent in cheese, evaporated milk or dry milk. Five ounces of American (Cheddar) cheese, or 1 qt. skim milk and 1½ oz. butter, or 3½ oz. dry skim milk and 1½ oz. butter, or 17 oz. evaporated milk are about equivalent to 1 qt. fluid whole milk.

[2] Such as green cabbage, kale, snap beans, carrots.

[3] Such as apples, bananas, peaches, onions, corn, celery.

[4] Exclude bacon and salt side.

[5] Count 1¼ lb. bread as 1 lb. flour. Use chiefly whole-grain or enriched products.

[6] Include bacon and salt side.

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Whether a family will choose to follow a low-cost or a more expensive type of diet will depend on income, how many persons the income must support and the importance the family attaches to food. However, the amount of money spent for food does not necessarily determine the adequacy of the diet. A family may follow a marketing list for the moderate-cost meals but fail to get its money's worth in food value. This may be due to poor planning, wasteful buying, improper care of food in the home or waste in preparing and cooking foods.

Nutrition workers often have the impression that those members of the population who need such advice most urgently will not take the time and trouble to apply the information which is available. One of the great merits of these Government bulletins is that the instruction about adequate diets is made simple and compatible with time and attention which any housewife can give. Again it is urged that these documents are the best investment which a few cents can secure for the family with limited income. The way in which the selection of an appropriate diet plan may be made to accord with the family income and the proportion to be devoted to food is dependent on the percentage of the family income that is allotted to food. Thus a family of two with a total annual income of $1,000 would have had to devote 25 per cent of the income to food in order to afford even the low cost diet at 1941 prices. A family of seven would have required an income of $2,900 for a similar diet at the 25 per cent allowance. Before this family of seven would be justified in attempting to use the moderate cost diet the income would have to be well over $4,000 annually. With food prices increasing since 1941 the handicaps are still greater. If the family budget will allow

devoting a higher proportion to purchase of food, a better diet can be secured for a given income.

Since it is estimated that the average family income in the United States in 1941 was between $1,200 and $1,500, the importance of the minimum cost and restricted diets may be realized. The alarming implications of postwar conditions on this entire picture are self-evident. For more than half the urban population of this country the moderate cost diet is out of the question. The liberal diet is available to only a minority of the citizens of the United States. At once the matter of adequate nutrition is seen to involve the questions of income, wage scale, limitation of family size and public assistance for the unemployed and unemployable. There is one important modifying factor in this discouraging picture. The family garden, the keeping of chickens or a cow and the raising and home-canning of fruits may contribute significant amounts of the important protective foods to the family table. This may make it possible to have minimum or moderate cost diets for homes where only the restricted diet would otherwise be possible. The physician should be alert to add his effort to that of many other agencies which are trying to increase domestic gardening and the use of dairy products. The decentralization of large urban populations will be necessary before this can be made to apply to that concentrated fraction of the population of modern America. This dependence on garden, orchard and dairy products raised on the home grounds makes the application of the tabulated data to agricultural families impossible. It would be ex-

tremely difficult to introduce cash allowances for domestic production into such a table because of the various types and amounts of such activity. This difficulty does not apply to the detailed advice about the menus and selection of foods which have already been outlined.

There are plenty of problems to face in putting nutrition knowledge to work in this country. Not the least of these result from low incomes. Many families just do not have enough cash income to buy the right kind of food and they may not live where they can earn this. Several federal agencies have been attacking this phase of the problem in practical ways. The school lunch program, sponsored and administered by local community agencies, provided one good meal a day for 4,000,000 children last year, and this year is being expanded to reach many more. Low-cost milk is provided in many communities for families who cannot afford the prevailing price. The Food Stamp Plan is being extended to more cities, so that families on relief may make their food dollar go farther toward providing the right food for their families. Wherever state or local nutrition committees recognize the need for introduction or expansion of such programs, they have made every effort to encourage them and cooperate in the projects.

There are also problems of food production and distribution. The relating of agricultural production to the physiological needs of the population comes nearer to being a reality today than at any time since the League of Nations Joint Committee first discussed agricultural planning in relation to nutrition in 1935. The idea was sound then, but few would listen. The United States is today trying to apply that principle. In the new agricultural production program Secretary Wickard has asked American farmers to produce more food, especially protective foods—milk, meat, eggs, vegetables, fruits. These are the same foods which have always been stressed in home-production programs.[4]

[4] From "Our Own Nutrition Problems," by Helen S. Mitchell, Principal Nutritionist, Office of Defense, Health and Welfare Services, in *Journal of the American Dietetic Association*, 18:9-11, January, 1942.

Although this quotation is somewhat outdated, it indicates some of the care and planning which had reached the stage of practical function at the time of the entrance of the United States into the war. The Food Stamp Plan is no longer a live issue, inasmuch as it was organized chiefly to assist in the intelligent disposal of surpluses of agricultural commodities.

One of the few real advantages that may eventually be considered to have accrued to the world from World War II is an accentuation of the awareness of malnutrition the world over, as evidenced by the growing Food and Agricultural Organization of international scope. The weight of the UNRRA program has been felt throughout the war-torn countries of the world, and its effect in preventing mass starvation is incalculable. In the years to come we may confidently expect an increase in number and efficiency of such agencies, which must be properly integrated and co-ordinated if they are to be most effective. The emphasis of the nutrition worker and of the physician must necessarily be on the needs of the individual. The production of foods must be geared to human needs for food. Concerted approach to this enormous problem is required of persons in a great variety of professions. It is the purpose of this brief discussion to present some basic information as well as to stimulate interest, if possible, in the public health aspect of malnutrition which, as an international problem, is tightly interwoven with the economic structure of the world. Physicians may rightfully be expected to contribute some leadership to the solution of this perplexing situation.

APPENDIX

COMMERCIAL PREPARATIONS

It is manifestly impossible even to attempt to list the large number of excellent vitamin preparations on the market at the present time. However, certain general statements concerning the various individual vitamins may serve a useful purpose in assisting the physician in prescribing these dietary supplements.

VITAMIN A.—Vitamin A is available in many different forms, the cheapest of which is probably one of the various fish liver oils. In this form it accompanies vitamin D. The United States Pharmocopeia requires each gram of cod liver oil to contain at least 850 U. S. P. units (I. U.) of vitamin A and 85 U. S. P. units of vitamin D. Vitamin A is obtainable in the following preparations:

1. Cod liver oil (all brands): Vitamin A potency 850 U. S. P. units per Gm.; vitamin D potency 85 U. S. P. units per Gm.

2. Cod liver oil concentrates: In liquid form the concentration may be as high as 60,000 U. S. P. units of vitamin A and 8,000 U. S. P. units of vitamin D per Gm. Capsules and tablets contain 3,150 U. S P. units of vitamin A and 315 U. S. P. units of vitamin D.

3. Halibut liver oil: Minimum potency for vitamin A, 60,000 U. S. P. units per Gm.; vitamin D, 600 U. S. P. units per Gm.

4. Halibut liver oil capsules: Each capsule contains either 5,000 or 25,000 U. S. P. units of vitamin A.

5. Oleovitamin A (fish liver oil or vitamin A concentrate diluted with edible vegetable oil): Each capsule contains either 5,000 or 25,000 U. S. P. units. Each gram of oil contains not less than 50,000 and not more than 65,000 U. S. P. units.

6. Oleovitamin A capsules: Each capsule contains either 5,000 or 25,000 U. S. P. units.

7. Shark liver oil: Each gram of oil contains not less than 16,500 U. S. P. units of vitamin A and 40 U. S. P. units of vitamin D.

In addition, pure vitamin A (from fish liver oils) is available in capsules up to 100,000 U. S. P. units each in potency.

Vitamin A concentrates are preferably kept at refrigerator temperatures.

THIAMINE.—In pure form thiamine is available in both tablet and liquid form, the latter for parenteral injection. The smallest tablet contains 1.0 mg. (330 I. U.). Larger tablets are also available, but the thiamine content is always clearly stated. In addition, solutions of any desired strength are readily prepared because of the high solubility of this compound. Thiamine preparations are all stable and may be kept without difficulty.

RIBOFLAVIN.—Riboflavin may be obtained in pure form in tablets containing from 1 to 5 mg. each. In dry form it is not easily destroyed by diffuse light. Solutions are completely inactivated by sunlight. Riboflavin is quite insoluble in water but soluble in dilute alkalis.

NIACIN—NICOTINIC ACID.—This vitamin is available in tablets of varying size, the minimum being 20 mg. The 50 and 100 mg. sizes are most convenient for the treatment of clinical deficiency states. Solutions for parenteral injection may also be obtained. All preparations of nicotinic acid are stable and will keep indefinitely.

NIACINAMIDE.—The amide form is interchangeable with nicotinic acid so far as potency is concerned. It lacks the vasodilating effect of the latter. It is available in the same form as niacin and is gradually replacing it because of freedom from side-reactions.

PYRIDOXINE.—Even though the function of this vitamin remains unknown, the pure synthetic compound is commercially available in solutions of varying strength. Vials containing from 1 to 5 Gm. may be obtained. The preparation is stable.

PANTOTHENIC ACID.—This vitamin is available as calcium pantothenate, a highly water soluble salt. Vials of 1 to 5 Gm. may be obtained. The preparation is stable.

ASCORBIC ACID.—In pure form, vitamin C is available in tablets varying upward in potency from 25 to 50 and 100 mg. per tablet. Only the solid form is acceptable because of the instability of this vitamin, with the exception of solutions prepared in carefully buffered solvents and sealed in ampules, in which form the potency will be retained indefinitely, as is the case also with tablets.

VITAMIN D.—In addition to the preparations of fish liver oils mentioned under vitamin A, which also contain vitamin D, the following are recognized:

1. Drisdol: A solution of vitamin D_2 in ethylene glycol with a potency of 250 U. S. P. units per drop.

2. Halibut liver oil with vitamin D concentrate: The potency is not less than 59,000 U. S. P. units of vitamin A and 5,500 U. S. P. units of vitamin D per Gm. Each capsule contains 10,000 U. S. P. units of vitamin A and 945 U. S. P. units of vitamin D.

3. Halibut liver oil with viosterol: Assayed potency is 44,800 U. S. P. units of vitamin A and 10,000 U. S. P. units of vitamin D per Gm. minimum.

4. Concentrated oleovitamin A and D: Its assayed potency is not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A and not less than 10,000 and not more than 13,000 U. S. P. units of vitamin D per Gm. Capsules contain 5,000 U. S. P. units of vitamin A and 1,000 U. S. P. units of vitamin D.

5. Viosterol: Synthetic vitamin D_2 obtained from activated ergosterol prepared to a minimum potency of 10,000 U. S. P. units per Gm.

VITAMIN E.—Pure tocopherol preparations are available, from both natural and synthetic sources, in capsules varying from 3 to 50 mg. each. In addition, wheat germ oil has vitamin E potency, usually varying from 3 to 5 Evans-Burr units per Gm.

VITAMIN K.—Menadione is commercially available for both oral and parenteral use. The vials and tablets contain either 1 or 2 mg. corresponding to the well established therapeutic dose.

Mixtures of Vitamins.—There are a great many types of vitamin mixtures available to both the physician and the layman. Some of these are simple combinations in various proportions of synthetic vitamins, while others are concentrates of naturally occurring substances. Because of the wide variation in composition of these various preparations, no statement can be made which will cover all cases. In general, however, it seems wisest to recommend their use for the fortification of an otherwise slightly inadequate diet rather than to suggest their application to the therapy of serious clinical deficiency diseases. Most of them do specify, and all should specify, the exact potency of each constituent. On this basis alone can judgment be passed as to their efficacy under varying circumstances.

The mixtures may be grouped into three types: fat-soluble vitamins, chiefly A and D, water-soluble vitamins, chiefly the

B group, and preparations of all vitamins from A to D, and sometimes E. Use of this last type of mixed fat- and water-soluble vitamins seems inadvisable for prescription for almost any patient. Even a simple dietary history will indicate whether the patient needs augmentation of A and D, or the B group, or ascorbic acid. Almost no diet worth the name will be deficient in all. Therefore the specific needs had best be met by appropriate prescription. The preparation of such mixtures of all possible vitamins has led to the marketing of a bewildering variety of competing tablets and capsules, making vitamin prescription seem easy enough to eliminate thinking by the physician. But as one consequence, the multitude of products, made up with from five to 10 variables, cannot be compared accurately as to potency purchased per dollar. Intelligent and economical prescribing of these mixtures is impossible. A false sense of security is apt to follow the use of tablets which contain many vitamins but which may provide too little of any one to meet real needs. Such mixtures are therefore discussed only to be condemned.

The association of vitamins A and D is entirely different. These occur together in many natural sources. A growing tendency is apparent, aided by recent control rulings by the United States Food and Drug Administration, to limit the amount of vitamin A per capsule or dose to 5,000 units. The conventional capsules on the market soon will be of this potency, with 500 or more units of D, when the mixture is desired. This may be assumed to provide a safe daily maintenance allowance for child or adult. Multiple doses of this type may be prescribed for therapy of patients with marked deficiency. One capsule daily will be dependable for maintenance if the diet is limited in fats. Higher potency materials are still available, especially with larger doses of vitamin D, limiting the amount of vitamin A to 5,000 units.

The mixtures of the B group vary so much in the absolute amounts of the individual fractions and in the proportions of these separate vitamins that comparisons as to nutritive and economic advantages are difficult. By joint efforts of the several regulatory agencies, clarification is now under way providing that any fortification of either yeast or liver extracts shall have the total thiamine, riboflavin and nicotinic acid contents in the ratio of 1:2:10 mg. No rulings have been laid down about the other components of the B complex, pending the determination of their qualitative and quantitative signifi-

cance in human beings. When this convention becomes generally used it will be easier to compare the costs of doses which will provide 1 mg. of thiamine and the other two vitamins in the accepted ratio. This will reduce the problem of the physician who desires to select the best B complex tablet or capsule, whether to prevent deficiency in association with greatly restricted diets or to supplement an adequate diet of a patient who has a preexisting deficiency. Until the clinical values of pantothenic acid, pyridoxine, choline, biotin and the other factors in the B group have been demonstrated, it is urged that vitamin B complex preparations be selected on the basis of the cost of thiamine, riboflavin and nicotinic acid in the 1:2:10 ratio.

LABORATORY METHODS OF ASSAY FOR DEFICIENCY DISEASES

Vitamin A.—All of the methods for chemical determination of vitamin A and carotene in biologic material depend on the Carr-Price antimony trichloride reaction. The best adaptation of this reaction to clinical problems is that of M. S. Kimble, *Journal of Laboratory and Clinical Medicine* 24:1055, July, 1939. It is adaptable to the needs of any clinical group, but it requires the use of a good photo-electric colorimeter.

Thiamine.—Several methods have been successfully adapted to the clinical determination of thiamine. Most widely used is probably the thiochrome method with various adaptations, and of these the one devised by Hennessy (*Industrial and Engineering Chemistry* [analytical ed.] 13:216, 1941) is probably the best. It is extremely sensitive and involves the use of a good fluorophotometer. After some experience with the technic, from eight to 20 analyses in duplicate can be performed daily.

Slightly less sensitive and somewhat more time-consuming is the colorimetric method of Melnick and Field (*Journal of Biological Chemistry* 130:97, September, 1939). It is accurate and checks well with biologic assays.

Riboflavin.—An excellent method for the determination of riboflavin in urine and blood is that of Snell and Strong, *Industrial and Engineering Chemistry* (analytical edition) 11:346, 1939. It is a microbiologic method which depends on the acid production of Lactobacillus casei. It is dependable, quick and applicable to clinical studies and requires the services of a trained bacteriologic technician.

Nicotinic Acid.—The analysis by chemical methods of biologic materials for their content of nicotinic acid is complicated by the presence, under most conditions, of trigonelline, which is a product of the metabolism of nicotinic acid. While no simple easy method for this determination is available, that of Perlzweig, Levy and Sarett (*Journal of Biological Chemistry* 136:729, December, 1940) as modified by Sarett, Huff and Perlzweig (*Journal of Nutrition* 23:23, January, 1942) is probably the most promising. The technic is sufficiently complicated to deprive the method of widespread clinical value.

PYRIDOXINE.—A satisfactory method of analysis of biologic materials has been developed by Scudi (*Journal of Biological Chemistry* 139:707, June, 1941). It gives accurate results and is applicable to clinical problems.

PANTOTHENIC ACID.—A slight modification of the riboflavin method of Snell and Strong makes it applicable to the determination of pantothenic acid in urine. This method, using a microbiologic technic, has been carefully studied by Strong, Feeney and Earle (*Industrial and Engineering Chemistry* [analytical ed.] 13:566, 1941). It is an accurate method suitable for clinical use.

ASCORBIC ACID.—The method of Mindlin and Butler as modified by Bessey (*Journal of Biological Chemistry* 126:771, December, 1938) is well adapted to blood analysis. It depends on decolorization of the dye 2,6 dichlorophenolindophenol and requires the use of a good photo-electric colorimeter. Results are accurate and dependable. A microtitration method which is slightly less accurate is that of Farmer and Abt (*Proceedings of the Society for Experimental Biology and Medicine* 34:146, March, 1936).

VITAMIN D.—Since no assay methods are available for vitamin D itself, the necessary criteria of deficiency can be obtained by chemical estimation of calcium, phosphorus and phosphatase in blood. The first two are usually standard determinations for good clinical laboratories. For blood phosphatase, the method of Bodansky (*Journal of Biological Chemistry* 101:93, June, 1933) is recommended.

VITAMIN E.—No methods of estimation are available.

VITAMIN K.—Vitamin K content of body fluids is not estimated directly, but the end-result of K deficiency can easily be estimated by determination of prothrombin time of blood. The method recommended is that of Quick as modified by F. J. Pohle and J. K. Stewart (*American Journal of the Medical Sciences* 198:622, November, 1939). It is easily within reach of most hospital laboratories.

NUTRITIVE VALUE OF 100 GM. SELECTED FOODS, EDIBLE PORTION*

Food item	Water	Food energy	Protein	Fat	Carbo-hydrate	Calcium	Phos-phorus	Iron	Vitamin A value	Thiamine	Ribo-flavin	Niacin	Ascorbic acid
	Percent	Calories	Grams	Grams	Grams	Milligrams	Milligrams	Milligrams	International Units	Milligrams	Milligrams	Milligrams	Milligrams
MILK, CREAM, ICE CREAM, CHEESE													
Milk:													
1. Buttermilk, cultured	90.5	35	3.5	0.1	5.1	(118)	(93)	(0.07)	(Trace)	(0.04)	(0.18)	(0.1)	(1)
2. Chocolate flavored [1]	83.0	75	3.2	2.2	10.6	109	91	.07	90	.03	.16	.1	0
3. Condensed, sweetened	27.0	327	8.1	8.4	54.8	273	228	(.20)	(430)	(.05)	(.39)	(.2)	(1)
4. Dry skim	3.5	359	35.6	1.0	52.0	1,300	1,030	.58	(40)	.35	1.96	1.1	7
5. Dry whole	3.5	496	25.8	26.7	38.0	949	728	.58	1,400	.30	1.46	.7	6
6. Evaporated, unsweetened	73.7	139	7.0	7.9	9.9	243	195	.17	400	.05	.36	.2	1
7. Fresh skim	90.5	35	3.5	.1	5.1	(118)	(93)	(.07)	(Trace)	.04	(.18)	(.1)	(1)
8. Fresh whole	87.0	69	3.5	3.9	4.9	118	93	.07	(160)	.04	.17	.1	1
Cream; ice cream:													
9. Cream (20 percent), sweet or sour	72.5	208	2.9	20.0	4.0	(97)	(77)	(.06)	(830)	(.03)	(.14)	(.1)	(1)
10. Ice cream, plain [1]	62.0	210	4.0	12.3	20.8	132	104	.10	540	.04	.19	.1	Trace
Cheese:													
11. Cheddar type	39	393	23.9	32.3	1.7	873	610	(.57)	1,740	.04	.50	(.2)	(0)
12. Cottage	74.0	101	19.2	.8	4.3	82	263	(.46)	(30)	.02	.29	(.1)	(0)
13. Cream	53.3	367	7.1	36.9	1.7	(298)	(208)	(.17)	2,210	(.01)	.14	.1	(0)
14. *Processed; canned [2]	37.5	382	21.9	31.8	2.0	716	831	.76	1,260	.03	.43	.1	(0)
15. All other	(39)	393	(23.9)	(32.3)	(1.7)	(873)	(610)	(.57)	2,050	.04	.52	.2	(0)
FATS, OILS													
16. *Army spread, canned [3]	27.8	562	5.2	56.7	7.7	244	241	.5	2,820	.03	.19	.1	0
17. *Bacon, canned	12.6	704	7.9	74	1.6	14	39	.9	(0)	.26	.10	1.5	0
18. Bacon, medium fat	20	626	9.1	65	(1.1)	13	108	.8	(0)	(.42)	(.10)	(2.1)	0
19. Butter	15.5	733	.6	81	.4	16	16	.2*	[4]3,300	Trace	.01	.1	0
20. French dressing	38.3	423	.8	39	17.3	(5)	(5)	.1	0	0	0	0	0
21. Lard, other shortening	0	900	0	100	0	0	0	0	0	(0)	(0)	(0)	0
22. Margarine with vitamin A added	15.5	733	.6	81	.4	(2)	(15)	(.2)	[5](1,980)	(0)	(0)	(0)	0

Note: Asterisk indicates Army ration component; parentheses, imputed value.

[1] Calculated from ingredients.
[2] Cheddar type.
[3] Not less than 56 percent butter fat on dry solids basis; cheese curd, skim milk powder.
[4] Year-round average.
[5] Plain margarine is considered to have no vitamin A value.

*From *Tables of Food Composition*, U. S. Department of Agriculture Miscellaneous Publication no. 572, 1945.

Food item	Water	Food energy	Protein	Fat	Carbo-hydrate	Calcium	Phos-phorus	Iron	Vitamin A value	Thiamine	Ribo-flavin	Niacin	Ascorbic acid
	Percent	Calories	Grams	Grams	Grams	Milli-grams	Milli-grams	Milli-grams	Inter-national Units	Milli-grams	Milli-grams	Milli-grams	Milli-grams
FATS, OILS—Continued													
23. Mayonnaise	16	720	1.5	78	3.0	(19)	(60)	(1.0)	(210)	(0.04)	(0.04)	(0)	(0)
24. Salad dressing	44.7	391	1.1	36.8	13.9	(9)	(30)	(.4)	(140)	(.02)	(.03)	(0)	(0)
25. Salad or cooking oil	0	900	0	100	0	0	0	0	0	0	0	0	0
26. Salt pork, fat	8	781	3.9	85	0	2	42	.6	(0)	(.18)	(.04)	(.9)	0
EGGS													
27. Egg yolks fresh	49.4	355	16.3	31.9	.7	147	586	7.2	3,210	.32	.52	------	0
28. *Eggs, whole, dried	2	593	(43.2)	(43.3)	(2.6)	187	800	8.7	4,460	.35	1.23	.2	0
29. Eggs, whole, fresh	74.0	158	12.8	11.5	.7	54	210	2.7	1,140	.12	.34	.1	0
MEAT, POULTRY, FISH													
Beef:													
Thin—Utility, Grade C:													
30. Carcass; side, including kidney fat	66	201	18.8	14	0	11	203	2.8	(0)	.12	.15	5.1	0
Medium—Commercial, Grade B:													
31. Carcass; side, including kidney fat	60	268	17.5	22	0	10	189	2.6	(0)	.11	.14	4.7	0
32. Carcass trimmed to retail basis	63	235	18.2	18	0	11	196	2.7	(0)	.11	.14	4.9	0
33. *Chopped meat [6]	54	325	16.1	29	0	9	174	2.4	(0)	.10	.13	4.4	0
34. *Roasting meat [6]	67	193	18.9	13	0	11	204	2.8	(0)	.12	.15	5.1	0
35. *Stewing meat [6]	63	235	18.2	18	0	11	196	2.7	(0)	.11	.14	4.9	0
Fat—Good, Grade A:													
36. Carcass; side, including kidney fat	55	317	16.3	28	0	10	176	2.4	(0)	.10	.13	4.4	0
Very fat—Choice, Prime, Grade AA:													
37. Carcass; side, including kidney fat	47	406	13.7	39	0	8	148	2.1	(0)	.08	.11	3.7	0
Retail items; [7]													
38. Chuck roast (wholesale chuck)	65	218	18.6	16	0	11	200	2.8	(0)	.12	.15	5.0	0
39. *Corned beef, canned	57.3	232	24.4	15	0	29	113	4.0	(0)	.02	.19	2.7	0
40. Corned beef, medium	54.2	288	15.8	25	0	9	170	2.4	(0)	.05	.10	1.7	0
41. Dried or chipped	47.7	194	34.3	6.3	0	20	370	5.1	(0)	.11	.22	3.7	0

42. Hamburger	55	316	16	28	0	9	172	2.4	(0)	.10	.13	4.3	0
43. Loin steaks (wholesale loin)	57	293	16.9	25	0	10	182	2.5	(0)	.10	.13	4.6	0
44. Rib roast or steak (wholesale rib)	59	277	17.4	23	0	10	188	2.6	(0)	.11	.14	4.7	0
45. *Roast, canned	60.0	217	25	13	0	9	164	2.2	(0)	.02	.24	4.5	0
46. Round steak (wholesale round)	67	194	19.3	13	0	11	208	2.9	(0)	.12	.15	5.2	0
47. Rump roast (wholesale rump)	53	341	15.5	31	0	9	167	2.3	(0)	.10	.12	4.2	0
48. Soup meat (wholesale shanks)	70	162	20.3	9	0	12	219	3.0	(0)	.13	.16	5.5	0
49. Stew meat (73 percent lean)	53	333	15.8	30	0	9	170	2.4	(0)	.10	.12	4.3	0
Lamb: Carcass, side:													
50. Thin	66.3	202	17.1	14.8	0	10	184	2.6	(0)	.20	.25	5.6	0
51. Intermediate	55.8	312	15.7	27.7	0	9	169	2.4	(0)	.18	.23	5.2	0
52. Fat	46.2	410	13.0	39.8	0	8	140	2.0	(0)	.15	.19	4.3	0
Retail items, [7] intermediate grade:													
53. Leg roast (wholesale leg)	63.7	230	18.0	17.5	0	10	194	2.7	(0)	.21	.26	5.9	0
54. Shoulder roast (wholesale 3-rib shoulder)	58.3	290	15.6	25.3	0	9	163	2.3	(0)	.18	.23	5.2	0
55. Sirloin chop (wholesale leg)	63.7	230	18.0	17.5	0	10	194	2.7	(0)	.21	.26	5.9	0
Pork: Packers' carcass; side:													
56. Thin	50	371	14.1	35	0	8	152	2.1	(0)	.89	.18	3.8	0
57. Medium	42	453	11.9	45	0	7	128	1.8	(0)	.75	.15	3.2	0
58. Fat	35	534	9.8	55	0	6	106	1.5	(0)	.62	.12	2.6	0
59. Miscellaneous lean cuts [8]	52	352	14.5	32.7	0	8	156	2.2	(0)	.92	.18	3.9	0
Retail items: [7] Bacon. See Fats, Oils.													
60. Boston butt	60	273	16.6	23	0	10	179	2.5	(0)	1.05	.21	4.5	0
61. Ham, fresh	53	340	15.2	31	0	9	164	2.3	(0)	.96	.19	4.1	0
62. Ham, smoked	42	384	16.9	35	(.3)	10	182	2.5	(0)	.78	.19	3.8	0
63. Loin	58	291	16.4	25	0	10	177	2.5	(0)	1.04	.20	4.4	0
64. Picnic	52	347	14.8	32	0	9	160	2.2	(0)	.94	.18	4.0	0
65. Pork links; sausage	41.9	446	10.8	44.8	0	6	116	1.6	(0)	.22	.15	2.3	0
Salt pork. See Fats, Oils.													
66. Spareribs	53	346	14.6	32	0	8	157	2.2	(0)	.92	.18	3.9	0

NOTE: Asterisk indicates Army ration component; parentheses, imputed value.

[6] Average values for composition of all cuts in a boned and trimmed carcass of commercial grade generally used for (a) chopped meat, (b) roasting and broiling, (c) stewing and boiling.

[7] Values for fresh items are from the medium fat wholesale cuts considered to be nearest approximations for corresponding retail items.

[8] Lean cuts from medium fat carcass weighted according to civilian supply, 1944. Excludes bacon, lard, salt side, fat back.

NUTRITIVE VALUE OF 100 GM. SELECTED FOODS, EDIBLE PORTION—(Continued)

Food item	Water	Food energy	Protein	Fat	Carbo-hydrate	Calcium	Phos-phorus	Iron	Vitamin A value	Thiamine	Ribo-flavin	Niacin	Ascorbic acid
	Percent	Calories	Grams	Grams	Grams	Milli-grams	Milli-grams	Milli-grams	Inter-national Units	Milli-grams	Milli-grams	Milli-grams	Milli-grams
MEAT, POULTRY, FISH—Continued													
Veal:													
Carcass; side, excluding kidney fat:													
67. Thin....	71	151	19.7	8	0	11	212	3.0	(0)	0.18	0.28	6.5	0
68. Medium....	68	184	19.1	12	0	11	206	2.9	(0)	.17	.27	6.3	0
69. Fat....	65	218	18.5	16	0	11	199	2.8	(0)	.17	.26	6.1	0
Retail items, [7] medium fat:													
70. Chops (wholesale loin)....	69	176	19.2	11	0	11	207	2.9	(0)	.18	.27	6.3	0
71. Cutlet (wholesale round)....	70	159	19.5	9	0	11	210	2.9	(0)	.18	.28	6.4	0
72. Leg roast or steak (wholesale leg)....	(68)	186	(19.1)	(12.2)	0	11	206	2.9	(0)	.17	.27	6.3	0
73. Stew meat (74 percent lean)....	64	226	18.3	17	0	11	197	2.7	(0)	.17	.26	6.0	0
Variety meats; meat mixtures:													
74. Beef and gravy, canned [9]....	65.3	188	19.4	11.7	1.3	19	122	2.7	(30)	.09	.19	2.7	0
75. Bologna....	62.4	217	14.8	15.9	3.6	9	160	2.2	(0)	.31	.30	3.0	0
76. Chile con carne, without beans, canned [10]....	66.3	198	10.2	14.6	6.4	21	152	.7	160	.01	.10	2.1	0
77. Frankfurters....	64.3	201	15.2	14.1	3.3	9	164	2.3	(0)	.19	.23	2.4	0
78. Ham and eggs, canned [11]....	63.9	227	14.4	18.3	1.2	43	166	2.2	500	.16	.24	1.7	0
79. Hash, corned beef, canned [12]....	69.4	143	15.1	6.1	7.0	26	(90)	1.3	(0)	.02	.13	2.4	0
80. Hash, meat and vegetable, canned [13]....	73.3	122	10.0	5.0	9.3	14	(66)	1.2	(0)	.04	.11	2.5	6
81. Heart, fresh....	75.4	126	(16.5)	(6.3)	(.7)	10	236	6.2	(0)	.54	.90	6.8	14
82. Liver. fresh....	70.9	131	(19.8)	(4.2)	(3.6)	8	373	12.1	19,200	.27	2.80	16.1	31
83. Liver sausage....	59.0	258	16.7	20.6	1.5	9	238	5.4	(5,750)	.17	1.12	4.6	(0)
84. Luncheon meat, canned [14]....	56.3	270	15.2	22.5	1.7	21	170	1.4	(0)	.29	.21	2.7	0
85. Pork and gravy, canned [15]....	64.9	206	15.4	15.2	1.9	16	162	1.6	(0)	.19	.24	2.7	0
86. Pork sausage, bulk, canned....	57.0	280	16.0	24.0	0	17	131	2.2	(0)	.19	.21	2.8	0
87. Spaghetti with meat, canned [16]....	71.0	142	9.8	3.9	10.2	38	97	1.8	480	.02	.12	2.2	4
88. Stew, meat and vegetable, canned [17]....	72.9	127	11.6	5.5	7.8	36	(136)	1.4	1,780	.04	.12	2.4	0
89. Tongue, fresh, medium fat....	68	202	16.4	15	.4	30	119	6.9	(0)	.22	.27	5.0	0
90. Vienna sausage, canned....	64.1	210	16.0	16.2	0	19	(164)	.6	(0)	.07	.14	3.1	0

#	Food													
	Poultry:													
91.	Chicken, boned, canned	67.1	175	21.8	9.8	0	32	(218)	(1.9)	Trace	.01	.15	3.7	2
92.	Chicken, roasters [18]	66.0	194	20.2	12.6	0	16	218	1.9	Trace	.11	.18	8.6	----
93.	Turkey, medium fat [18]	58.3	263	20.1	20.2	0	23	320	3.8	Trace	.12	.19	7.9	----
	Fish and shellfish:													
94.	Cod	82.6	70	16.5	.4	0	18	189	.9	----	.04	.05	2.3	2
95.	Fish, miscellaneous, medium fat	77.2	98	19.0	2.5	0	21	218	1.0	----	.07	.07	4.2	(2)
96.	Oysters, solids and liquor	87.1	50	6.0	1.2	3.7	68	172	7.1	----	.18	.23	1.2	----
97.	Salmon, canned	67.4	169	20.6	9.6	0	67	286	1.3	[19]80	.03	.18	6.5	----
98.	Sardines, canned in oil, drained solids	57.4	207	25.7	11.0	1.2	35	365	1.8	290	.06	.12	5.2	0
99.	Sardines, canned in oil, total contents of can	47.1	331	21.1	27	1.0	29	299	1.5	710	.05	.10	4.3	0
100.	Shrimp, canned	73.3	82	17.8	.9	.9	(75)	(210)	(2.0)	60	.01	.03	1.9	0
101.	Tuna fish, canned, drained solids	57.7	217	27.7	11.8	0	34	290	1.7	70	.04	.13	10.6	0
102.	Tuna fish, canned, total contents of can	51.1	294	23.9	22.1	0	30	252	1.5	130	.04	.11	9.2	0
	DRY BEANS AND PEAS, NUTS													
	Dry beans and peas:													
103.	*Bean soup, navy, dehydrated [20]	7.2	332	17.6	1.2	62.7	(148)	(463)	(10.3)	(0)	.46	.22	2.4	1
104.	Beans, canned, baked	71.0	117	5.7	2.0	19.0	(49)	(154)	(3.4)	[21]70	.05	.05	.8	2
105.	Beans, common or kidney, dry seed	10.5	350	22.0	1.5	62.1	148	463	10.3	0	.60	.24	2.1	2
106.	Beans, lima, dry seed	12.6	341	20.7	1.3	61.6	68	381	7.5	0	.60	.24	2.1	2
107.	Chickpeas	10.6	369	20.8	4.7	60.9	92	375	7.1	Trace	.35	.15	1.4	(2)
108.	Cowpeas	10.6	351	22.9	1.4	61.6	80	450	7.8	0	.83	.23	2.2	2
109.	*Pea soup, dehydrated [22]	7.2	336	20.4	1.2	60.8	(73)	(307)	(6.0)	220	.62	.21	3.1	2
110.	Peas, split	10.0	354	24.5	1.0	61.7	73	397	6.0	370	.87	.29	3.0	2
111.	Soybeans, whole, mature	7.5	351	34.9	18.1	[23](12.0)	227	586	8.0	110	1.14	.31	2.1	Trace
	Soy flour; flakes; grits:													
112.	Low fat	11	246	44.7	1.1	[23](14.2)	265	623	13.0	70	1.10	.35	2.9	(0)
113.	Medium fat	9	283	42.5	6.5	[23](13.6)	244	610	13.0	110	.82	.34	2.6	(0)
114.	Full fat	9	375	35.9	20.6	[23](11.4)	105	553	12.1	140	.77	.28	2.2	(0)

NOTE: Asterisk indicates Army ration component; parentheses, imputed value. Values for fresh items are from the medium fat wholesale cuts considered to be nearest approximations for corresponding retail items.

9 90 percent beef, 10 percent tomato gravy.
10 Not less than 60 percent meat, not more than 8 percent cereals, seasonings.
11 50 percent ham, 50 percent whole eggs.
12 72 percent beef, 28 percent potatoes.
13 50 percent meat, 48 percent potatoes, 2 percent onions.
14 Pork.
15 90 percent pork, 10 percent gravy.
16 50 percent meat, 10 percent dry spaghetti, 30 percent tomato puree, 5 percent cheese, 5 percent onions.
17 50 percent meat, 15 percent potatoes, 15 percent carrots, 8 percent dry beans, 12 percent tomato puree.
18 Vitamin values based on muscle meat only.
19 Based on pink salmon. Canned red salmon may have a value several times higher.
20 Navy bean meal, farinaceous flour up to 15 percent.
21 Contributed by tomatoes.
22 Pea meal, farinaceous flour up to 15 percent.
23 "Available" carbohydrate.

Food item	Water	Food energy	Protein	Fat	Carbo-hydrate	Calcium	Phos-phorus	Iron	Vitamin A value	Thiamine	Ribo-flavin	Niacin	Ascorbic acid
	Percent	Calories	Grams	Grams	Grams	Milli-grams	Milli-grams	Milli-grams	Inter-national Units	Milli-grams	Milli-grams	Milli-grams	Milli-grams
DRY BEANS AND PEAS, NUTS—Continued													
Nuts:													
115. Almonds	4.7	640	18.6	54.1	19.6	254	475	4.4	0	0.25	0.67	4.6	Trace
116. Peanut butter	1.7	619	26.1	47.8	21.0	74	393	1.9	0	.20	.16	16.2	(0)
117. Peanuts, roasted	2.6	600	26.9	44.2	23.6	74	393	1.9	0	24 .30	.16	16.2	(0)
118. Pecans	3.0	747	9.4	73.0	13.0	74	324	2.4	50	.72	.11	.9	2
119. Walnuts, English	3.3	702	15.0	64.4	15.6	83	380	2.1	30	.48	.13	1.2	3
VEGETABLES													
Fresh:													
120. Asparagus	93.0	26	2.2	.2	3.9	21	62	.9	1,000	.16	.17	1.2	33
121. Beans, lima, green	66.5	131	7.5	.8	23.5	63	158	2.3	280	.25	.14	.9	32
122. Beans, snap	88.9	42	2.4	.2	7.7	65	44	1.1	630	.08	.10	.6	19
123. Beet greens	90.4	33	2.0	.3	5.6	25	45	3.2	6,700	.05	.17	.3	34
124. Beets	87.6	46	1.6	.1	9.6	27	43	1.0	20	.03	.05	.4	10
125. Broccoli	89.9	37	3.3	.2	5.5	130	76	1.3	3,500	.09	.21	.9	118
126. Brussels sprouts	84.9	58	4.4	.5	8.9	34	78	1.3	400	.11	(.06)	(.3)	94
127. Cabbage	92.4	29	1.4	.2	5.3	46	31	.5	80	.07	.06	.3	52
128. Carrots	88.2	45	1.2	.3	9.3	39	37	.8	12,000	.07	.06	.5	6
129. Cauliflower	91.7	31	2.4	.2	4.9	22	72	1.1	90	.10	.11	.6	69
130. Celery	93.7	22	1.3	.2	3.7	50	40	.5	0	.03	.04	.3	7
131. Chard	91.8	25	1.4	.2	4.4	26	38	4.0	2,800	.06	.13	.2	38
132. Collards	86.6	50	3.9	.6	7.2	249	58	1.6	6,870	.22	(.20)	(.8)	100
133. Corn, sweet, white or yellow	73.9	108	3.7	1.2	20.5	9	120	.5	27 390	.15	.14	1.4	12
134. Cucumbers	96.1	14	.7	.1	2.7	10	21	.3	28 0	.04	.09	.2	8
135. Dandelion greens	85.8	52	2.7	.7	8.8	187	70	3.1	13,650	.19	.14	(.8)	36
136. Eggplant	92.7	28	1.1	.2	5.5	15	37	.4	30	.07	.06	.8	5
137. Kale	88.6	50	3.9	.6	7.2	225	62	2.2	7,540	.12	.35	(.8)	115
138. Lettuce, headed	94.8	18	1.2	.2	2.9	22	25	.5	540	.06	.07	.2	8

No.	Food													
139.	Lettuce, all other	94.8	18	1.2	.2	2.9	62	20	1.1	1,620	.06	.07	.2	18
140.	Mustard greens	92.2	28	2.3	.3	4.0	220	38	2.9	6,460	.09	.20	.8	102
141.	Okra	89.9	39	1.8	.2	7.4	82	62	.7	740	.12	.10	.7	30
142.	Onions, mature	87.5	49	1.4	.2	10.3	32	44	.5	50	.03	.02	.1	9[29]
143.	Parsnips	78.6	83	1.5	.5	18.2	57	80	.7	0	.11	.09	.2	18
144.	Peas, green	74.3	101	6.7	.4	17.7	22	122	1.9	680	.36	.18	2.1	26
145.	Peppers, green	92.4	29	1.2	.2	5.7	11	25	.4	630	.07	.04	.4	120
146.	Potatoes	77.8	85	2.0	.1	19.1	11	56	.7	20	.11	.04	1.2	17
147.	Pumpkin	90.5	36	1.2	.2	7.3	21	44	.8	(3,400)	(.05)	(.08)	(.6)	8
148.	Radishes	93.6	22	1.2	.1	4.2	37	31	1.0	30	.04	.04	.1	24
49.	Rutabagas	89.1	41	1.1	.1	8.9	55	41	.4	330	.06	.06	.5	36
50.	Spinach	92.7	25	2.3	.3	3.2	[30]	55	3.0	9,420	.12	.24	.7	59
151.	Squash, summer	95.0	19	.6	.1	3.9	15	15	.4	260	.04	.05	1.1	17
152.	Squash, winter	88.6	44	1.5	.3	8.8	19	28	.6	4,950	.05	.08	.6	8
153.	Sweetpotatoes	68.5	125	1.8	.7	27.9	30	49	.7	7,700[31]	.10	.06	.7	22
154.	Tomatoes	94.1	23	1.0	.3	4.0	11	27	.6	1,100	.06	.04	.6	23
155.	Turnip greens	89.5	37	2.9	.4	5.4	259	50	2.4	9,540	.10	.56	.8	136
156.	Turnips	90.9	35	1.1	.2	7.1	40	34	.5	Trace	.06	.06	.5	28
	Canned:													
157.	Asparagus	93.6	21	1.6	.3	3.0	20	34	1.0	600[32]	.06	.09	.8	15
158.	Beans, lima	80.9	72	3.8	.3	13.5	27	73	1.7	130	.03	.05	.5	8
159.	Beans, snap	94.0	19	1.0	0	3.8	27	19	1.4	410	.03	.05	.3	4
160.	Beets	89.4	39	1.0	0	8.7	15	29	.6	20	.01	.03	.1	5
161.	Carrots	92.2	30	.5	.4	6.1	22	24	.6	12,000	.03	.02	.3	2
162.	Corn, white or yellow	80.5	77	2.0	.5	16.1	4	51	.5	200[27]	.02	.05	.8	5
163.	Peas, green	82.3	69	3.4	.4	12.9	25	67	1.8	540	.11	.06	.9	8
164.	Pumpkin	90.2	38	1.0	.3	7.9	(20)	(36)	(.7)	3,400	.02	.06	.5	(0)
165.	Sauerkraut	93.2	20	1.1	.2	3.4	(46)	(31)	(.5)	Trace	.03	.20	.2	18[33]
166.	Spinach	92.3	25	2.3	.4	3.0	34	33	1.6	6,790	.02	.08	.3	14

NOTE: Asterisk indicates Army ration component; parentheses, imputed value.

24 Based on peanuts without skins; when skins are included the thiamine value is higher.
25 118 mg.; may not be available because of presence of oxalic acid.
26 105 mg.; may not be available because of presence of oxalic acid.
27 Based on yellow corn; white corn contains only a trace.
28 Based on pared cucumber; unpared contains about 260 I. U. vitamin A per 100 gm.

29 Green bunching onions contain about 23 mg. ascorbic acid per 100 gm.
30 81 mg.; may not be available because of presence of oxalic acid.
31 If pale varieties only were used, value would be very much lower.
32 Based on green products; bleached products contain only a trace.
33 Drained solids only.
34 90 mg.; may not be available because of presence of oxalic acid.

Food item	Water	Food energy	Protein	Fat	Carbo-hydrate	Calcium	Phos-phorus	Iron	Vitamin A value	Thiamine	Ribo-flavin	Niacin	Ascorbic acid
	Percent	Calories	Grams	Grams	Grams	Milli-grams	Milli-grams	Milli-grams	Inter-national Units	Milli-grams	Milli-grams	Milli-grams	Milli-grams
VEGETABLES—Continued													
Canned—Continued:													
167. Tomato catsup	69.5	110	2.0	0.4	24.5	12	18	0.8	(1,880)	0.09	0.07	2.2	11
168. Tomato juice	93.5	23	1.0	.2	4.3	(7)	(15)	(.4)	1,050	.05	.03	.7	16
169. Tomato puree	89.2	40	1.8	.5	7.2	(11)	(37)	(1.1)	1,880	.09	(.07)	1.8	28
170. Tomatoes	94.2	21	1.0	.2	3.9	(11)	(27)	(.6)	1,050	.05	.03	.7	16
Dehydrated: [35]													
171. •Cabbage, unsulfited [36]	8.8	346	13.7	1.8	68.8	374	274	4.7	520	.41	.37	2.4	180
172. •Carrots	5.6	361	4.0	1.4	83.1	(242)	(102)	(5.9)	117,000	.29	.28	3.2	11
173. •Onions	9.9	350	10.1	1.0	75.2	158	256	3.1	20	.23	.15	1.1	37
174. •Potatoes	7.2	363	7.1	.7	82.0	25	103	3.7	(0)	.25	.10	4.8	26
175. •Sweetpotatoes	5.3	373	5.1	.9	86.1	(76)	(75)	(2.3)	21,900	.18	.14	1.9	34
FRUIT													
Fresh:													
176. Apples	84.1	64	.3	.4	14.9	6	10	.3	90	.04	.02	.2	5
177. Apricots	85.4	56	1.0	.1	12.9	16	23	.5	2,790	.03	.04	.7	4
178. Avocados	65.4	265	1.7	26.4	5.1	10	38	.6	290	.12	.15	1.1	16
179. Bananas	74.8	99	1.2	.2	23	8	28	.6	430	.09	.06	.6	10
Berries:													
180. Blueberries	83.4	68	.6	.6	15.1	16	13	.8	250	(.03)	(.07)	(.3)	16
181. Strawberries	90.0	41	.8	.6	8.1	28	27	.8	60	.03	.07	.3	60
182. Other berries	84.4	65	1.2	.8	13.2	36	34	.9	320	.03	(.07)	(.3)	23
183. Cantaloups	94.0	23	.6	.2	4.6	17	16	.4	37 3,420	.06	.04	.8	33
184. Grapefruit	88.8	44	.5	.2	10.1	17	18	.3	Trace	.04	.02	.2	40
185. Grapes	81.6	74	.8	.4	16.7	17	21	.6	80	.05	.03	.4	4
186. Lemons	89.3	44	.9	.6	8.7	(14)	(10)	(.1)	0	.04	Trace	.1	45
187. Limes	86.0	53	.8	.1	12.3	(14)	(10)	(.1)	0	(.04)	(Trace)	(.1)	27
188. Oranges	87.2	50	.9	.2	11.2	33	23	.4	(190)	.08	.03	.2	49
189. Peaches	86.9	51	.5	.1	12.0	8	22	.6	880	.02	.05	.9	9

No.	Food	Water	Food energy	Protein	Fat	Carbohydrate	Calcium	Phosphorus	Iron	Vitamin A	Thiamine	Riboflavin	Niacin	Ascorbic acid
190.	Pears	82.7	70	.7	.4	15.8	13	16	.3	20	.02	.04	.1	4
191.	Pineapples	85.3	58	.4	.2	13.7	16	11	.3	130	.08	(.02)	(.2)	24
192.	Plums	85.7	56	.7	.2	12.9	17	20	.5	350	.15	(.03)	.6	5
193.	Rhubarb	94.9	18	.5	.1	3.8	38	25	.5	30	.01		.1	9
194.	Tangerines; other mandarin type oranges	87.3	50	.8	.3	10.9	(33)	(23)	(.4)	(420)	.07	(.03)	(.2)	31
195.	Watermelons	92.1	31	.5	.2	6.9	7	12	.2	590	.05	.05	.2	6
	Canned:													
196.	Apples; applesauce	79.8	80	.2	.1	19.7	(4)	(6)	(.2)	(60)	.01	.01	Trace	1
197.	Apricots	77.3	89	.6	.1	21.4	(10)	(15)	(.3)	1,350	.02	.02	.3	4
198.	Cherries	78.1	86	.6	.1	20.8	(11)	(14)	(.3)	(430)	.03	.02	.2	3
199.	Cranberry sauce	48.1	209	.1	.3	51.4	(8)	(7)	(.3)	(30)		(.04)		2
200.	Fruit cocktail	(80.6)	78	(.4)	(.2)	(18.6)	(9)	(12)	(.4)	160	.01	.01	.4	2
201.	Grapefruit juice	89.4	41	.5	.2	9.4	8	12	.4	Trace	.03	.02	.2	35
202.	Grapefruit segments	79.8	81	.6	.2	19.1	13	14	.3	Trace	.03	.02	.2	30
203.	Orange juice	86	55	.6	.1	12.9	(33)	(23)	(.4)	(100)	.07	.02	.2	42
204.	Peaches	80.9	75	.4	.1	18.2	(5)	(14)	(.4)	450	.01	.02	.7	4
205.	Pears	81.1	75	.2	.1	18.4	(8)	(10)	(.2)	Trace	.01	.02	.1	2
206.	Pineapple juice	86.2	54	.3	.1	13.0	15	8	.5	80	.05	.02	.2	9
207.	Pineapples	78.0	87	.4	.1	21.1	29	7	.6	80	.07	.02	.2	9
208.	Plums; Italian prunes	78.6	84	.4	.1	20.4	8	12	1.1	(230)	.03	.03	.4	1
	Dried:													
209.	*Apple nuggets	1.6	390	1.4	1.0	93.9	24	42	4.1	(0)	.05	.08	.5	11
210.	Apricots 39	24	292	5.2	.4	66.9	86	119	4.9	7,430	.01	.16	3.3	12
211.	*Cranberries	4.9	409	2.9	6.6	84.4	82	22	3.4	660	.19	.18	.9	33
212.	Peaches 39	24	295	3.0	.6	69.4	44	126	6.9	3,250	.01	.20	5.4	19
213.	Prunes 40	24	299	2.3	.6	71.0	51	85	3.9	1,890	.10	.16	1.7	3
214.	Raisins 40	24	298	2.3	.5	71.2	78	129	3.3	50	.15	.08	.5	Trace
	Synthetic fruit powders, canned:													
215.	*Grape juice 41	.2	42 250	.1	.5	3.1	132	65	.1	(0)	0	(0)	(0)	600
216.	*Lemon juice 43	1.7	42 336	.4	.3	60.8	60	33	1.5	(0)	(0)	(0)	(0)	876
217.	*Orange juice 44	1.9	42 341	1.1	.2	65.1	180	101	2.2	(0)	(0)	(0)	(0)	927

NOTE: Asterisk indicates Army ration component; parentheses, imputed value.

35 Freshly dehydrated products; some loss of vitamins is to be expected during storage.
36 If sulfited, the thiamine value would be much lower, and the ascorbic acid value would be about double.
37 Based on deeply colored varieties.
38 51 mg.; may not be available because of presence of oxalic acid.
39 Sulfured.
40 Unsulfured.
41 Citric acid, dextrose, coloring, flavoring, ascorbic acid.
42 Calorie value of organic acids included.
43 Powdered lemon juice and corn sirup, dextrose, citric acid, oil of lemon, ascorbic acid.
44 Powdered orange juice, lemon juice, and corn sirup, dextrose, citric acid, oil of orange, ascorbic acid.

Nutritive Value of 100 Gm. Selected Foods, Edible Portion—(Continued)

Food item	Water	Food energy	Protein	Fat	Carbohydrate	Calcium	Phosphorus	Iron	Vitamin A value	Thiamine	Riboflavin	Niacin	Ascorbic acid
	Percent	Calories	Grams	Grams	Grams	Milligrams	Milligrams	Milligrams	International Units	Milligrams	Milligrams	Milligrams	Milligrams
GRAIN PRODUCTS													
Flour, meal:													
Corn meal:													
218. White, degerminated	12	355	7.5	1.1	78.8	10	140	1.0	(0)	0.16	0.09	0.9	0
219. White, whole-grain	12	365	9.1	3.7	73.9	18	248	2.7	(0)	.41	.12	1.7	0
220. Yellow, degerminated	12	356	8.3	1.2	78.0	10	140	1.0	300	.15	.06	.9	0
221. Yellow, whole-grain	12	365	9.1	3.7	73.9	18	276	2.7	510	.45	.17	2.1	0
222. Cornstarch	12	352	.5	.2	87.0	Trace	Trace	Trace	(0)	(0)	(0)	(0)	0
Flour:													
223. Buckwheat, light	12	354	6.3	1.1	79.7	11	88	1.0	(0)	45 .31	45 .08	45 2.1	0
224. Rye, light	11	358	8.9	.9	78.5	18	278	1.3	(0)	.15	.07	.9	0
225. Rye, whole-grain	10	361	11.2	1.7	75.2	61	369	4.8	(0)	.47	.21	1.7	0
Soy. See Dry Beans and Peas.													
226. Wheat, patent	12	355	10.8	.9	75.9	19	93	.7	(0)	.07	.03	.8	0
227. Wheat, patent, enriched	12	355	10.8	.9	75.9	19	93	(2.9)	(0)	(.44)	(.26)	(3.5)	0
228. Wheat, self-rising	12	340	10.2	.9	72.9	220	330	.6	(0)	.02	.02	.7	0
229. Wheat, self-rising, enriched	12	340	10.2	.9	72.9	220	330	(2.9)	(0)	(.44)	(.26)	(3.5)	0
230. Whole wheat	11	360	13.0	2.0	72.4	38	385	3.8	(0)	.56	.12	5.6	0
Baked goods:													
Bread:													
231. Rye, light	37.6	263	(6.4)	(3.4)	(51.7)	(22)	(96)	(.3)	(0)	.16	(.04)	(1.1)	0
232. White, enriched	35.9	261	8.5	2.0	52.3	(56)	(100)	(1.8)	(0)	(.24)	(.15)	(2.2)	0
233. Whole wheat	37.	262	9.5	3.5	48.0	(60)	370	2.6	(0)	.28	.15	3.5	0
234. Cake, light batter type	26.8	327	6.4	8.2	57.0	62	(126)	2.0	------	.03	.10	.7	0
235. Cookies, assorted, plain	4.8	438	6.0	12.7	75.0	(22)	(65)	(.6)	(0)	(.04)	(.04)	(.5)	0
236. Cracker meal; crackers, assorted	4.5	422	9.5	10.3	72.7	22	102	1.5	(0)	(.07)	(0)	(.6)	0
237. Crackers, graham	5.5	419	8.0	10.0	74.3	20	203	1.9	(0)	.30	.12	1.5	0
238. Fig bars	13.8	363	4.2	4.8	75.8	(69)	(69)	(1.3)	(0)	(.02)	(.06)	(.9)	0
239. Pie, apple	------	266	(2.9)	(9.6)	(42.0)	(11)	(22)	1.9	(0)	(.05)	(.04)	.4	(0)
240. Pie, cream	------	223	(2.8)	(9.8)	(31.0)	20	(38)	.5	(0)	.03	.08	.2	(0)
241. Rolls, plain, enriched	29.4	304	8.2	6.1	54.1	(56)	(100)	(1.6)	(0)	(.24)	(.15)	(2.2)	0
242. Rolls, sweet, uncriched	29.6	304	7.8	5.4	56.0	(56)	(100)	.5	(0)	.08	.13	.8	0

Breakfast cereals:

No.	Item	Water	Food energy	Protein	Fat	Carbohydrate	Calcium	Phosphorus	Iron	Vitamin A	Thiamine	Riboflavin	Niacin	Ascorbic acid
243.	Corn flakes	9.3	359	7.9	.7	80.3	(10)	58	(1.0)	(0)	(.16)	.08	1.6	0
	Corn flakes, restored. See page 4.													
244.	Oatmeal	8.3	396	14.2	7.4	68.2	54	365	5.2	(0)	.55	.14	1.1	0
245.	Rice flakes; puffed rice	8.9	363	7.2	.4	82.6	(9)	(92)	.9	(0)	(.05)	(.03)	(1.4)	0
	Rice flakes; puffed rice, restored. See page 4.													
	Wheat cereals:													
246.	Farina	11	359	11.5	1.0	76.1	21	125	.8	(0)	.06	.06	1.0	0
247.	Farina, enriched	11	359	11.5	1.0	76.1	21	125	(1.3)	(0)	(.37)	(.26)	(1.3)	0
248.	Flakes; puffed wheat	6.2	372	11.9	1.5	77.7	33	353	3.7	(0)	.15	.12	4.2	0
	Flakes; puffed wheat, restored. See page 4.													
249.	Shredded wheat	7.7	369	10.4	1.4	78.7	(38)	(355)	(3.8)	(0)	.20	.14	4.2	0
250.	Whole-grain, uncooked	8.7	368	11.7	2.0	75.8	38	385	3.8	(0)	.45	.13	4.6	0
	Other cereals:													
251.	Barley, pearled, light	11.1	357	8.2	1.0	78.8	16	189	(2.0)	(0)	.12	.08	3.1	0
252.	Hominy	11.4	357	8.5	.8	78.9	11	70	1.0	(0)	.15	.05	(.0)	0
253.	Macaroni; spaghetti	11	360	13	1.4	73.9	22	144	1.2	(0)	.13	.08	2.1	0
254.	Noodles	9.1	385	14.3	5.0	70.6	24	156	1.9	(200)	(.13)	(.12)	(2.1)	0
	Rice:													
255.	Brown	12.0	356	7.5	1.7	77.7	39	303	5.5	(0)	.29	.05	4.6	0
256.	Converted	(12.3)	351	(7.6)	(.3)	(79.4)	(9)	(92)	(.7)	(0)	.23	.04	3.8	0
257.	White	12.3	351	7.6	.3	79.4	0	92	.7	(0)	.05	.03	1.4	0
258.	Tapioca	12.6	350	.6	.2	86.4	12	12	(1.0)	(0)	0	(0)	(0)	0
	SUGARS, SWEETS													
259.	Honey	20	319	.3	0	79.5	5	16	.9	(0)	Trace	.04	.2	4
260.	Jams; marmalades	28	298	.5	.3	70.8	12	12	(.3)	10	.02	.02	.2	6
261.	Jellies	34.5	261	.2	0	65.0	(12)	(12)	(.3)	(10)	(.02)	(.02)	(.2)	4
262.	Molasses, cane	24	240	(0)	(0)	(60)	273	51	6.7	(0)	.08	.16	2.8	(0)
263.	Sirup, table blends	25	206	(0)	(0)	(74)	46	16	4.1	(0)	0	.01	.1	(0)
264.	Sugar, brown	3	382	(0)	(0)	(95.5)	[46] 76	[46] 37	2.6	0	(0)	(0)	(0)	(0)
265.	Sugar, granulated or powdered	.5	398	(0)	(0)	99.5	(0)	(0)	.1	(0)	(0)	(0)	(0)	0

NOTE: Asterisk indicates Army ration component; parentheses, imputed value.

[45] Whole-grain buckwheat flour has approximately 0.61 mg. thiamine; 0.16 mg. riboflavin; and 4.2 mg. niacin per 100 gm.

[46] Based on dark brown sugar; lower values for light brown sugar.

Nutritive Value of 100 Gm. Selected Foods, Edible Portion—(Continued)

Food item	Water	Food energy	Protein	Fat	Carbo-hydrate	Calcium	Phos-phorus	Iron	Vitamin A value	Thiamine	Ribo-flavin	Niacin	Ascorbic acid
	Percent	*Calories*	*Grams*	*Grams*	*Grams*	*Milli-grams*	*Milli-grams*	*Milli-grams*	*Inter-national Units*	*Milli-grams*	*Milli-grams*	*Milli-grams*	*Milli-grams*
MISCELLANEOUS													
266. *Bouillon cubes	(3)	259	17.7	0	47.0	40	510	9.2	(0)	0.03	0.83	47.6	(0)
267. Chocolate, unsweetened	2.3	570	(5.5)	52.9	(18)	48	343	2.5	(0)	Trace	.24	1.1	(0)
268. Cocoa	4.3	329	(9.0)	18.8	(31.0)	49	700	2.7	(0)	Trace	(.39)	(2.3)	(0)
269. Coconut, dry, shredded	3.3	579	3.6	39.1	53.2	43	191	3.6	0	Trace	Trace	Trace	(0)
270. Gelatin dessert powder	1.6	392	9.4	0	88.7	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
271. Olives, green	75.2	144	1.5	13.5	4.0	101	15	2.0	420	Trace	----	Trace	7
272. Pickles, cucumber	95.2	11	.5	.2	1.9	24	22	.9	190	.01	.02	Trace	(0)
273. Wheat germ	11.0	389	25.2	10.0	49.5	84	1,096	8.1	(0)	2.05	.80	4.6	(0)
274. Yeast, compressed, baker's	70.9	109	13.3	.4	13.0	25	605	4.9	(0)	.45	2.07	28.2	(0)
275. Yeast, dried, brewer's	7.0	348	46.1	1.6	37.4	106	1,893	18.2	(0)	9.69	5.45	36.2	(0)

Note: Asterisk indicates Army ration component; parentheses, imputed value.

47 Based on vegetable extract type; meat extract type may have up to 27.0 mg. of niacin per 100 gm.

48 95 mg.; may not be available because of presence of oxalic acid.

49 160 mg.; may not be available because of presence of oxalic acid.

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